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THE DYNAMICS OF HYPERTENSION*

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HYPERTENSION, like other diseases, represents an experiment which nature performs on human beings. Physicians are concerned, not merely with the problem of establishing the existence of hypertension, but also with that of interpreting the kind of experiment going on, to the end that the human experiment may be terminated or that the natural compensatory mechanisms may be aided. Physicians have been helped in these tasks by applying information gained through an orderly solution of fundamental problems regardless of their practical importance. They have likewise been assisted through use of apparatus designed and tested in laboratories. But this has proved inadequate, hence the efforts to hasten our understanding of the hypertension problem by more pertinent types of animal experimentation. Now, observations and data gained from such experiments, and also from patients, again raise problems which need to be referred to laboratories of fundamental science for reinterpretation or additional study.

Our greatest and perhaps only hope of elucidating and alleviating human hypertension rests on such shuttling of problems between the clinics and laboratories of basic experimental sciences. Those who are attempting to curb or prevent animal experimentation in any of these fields by law should reflect on the impossibility of abrogating nature's hypertension experiments by similar legislative action.

EXPERIMENTAL AND CLINICAL HYPERTENSION

Persistent experimental hypertension can be produced, among other ways, (1) by midbrain lesions, e.g., by intracisternal injection of kaolin,

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(2) by section of all known moderator nerves, or (3) by damage to the kidneys, through ligation of ureters, by permanent constriction of the renal vessels, etc.

The last-named procedure, which we owe to Goldblatt and his associates,[1, 2, 3] is the most certain method yet devised for producing a persistent form of hypertension. Section of all the moderator nerves likewise causes a prolonged hypertension. But certainly it is not permanent unless all of the moderator nerves are cut, and even under these conditions it apparently fails occasionally.[4, 5] This suggests either that very few filaments suffice to stabilize blood pressure or, more probably, that direct cardiovascular compensations are adequate to re-establish normal pressure levels. In contrast to the hypertension induced by renal ischemia, which is not prevented or abolished by denervation of the kidney, by section of the splanchnic nerves, excision of the lower four thoracic ganglia, section of the sixth dorsal to second lumbar anterior roots, total sympathectomy, or destruction of the spinal cord, this form is prevented or abrogated by total sympathectomy or removal of all thoracic and sympathetic ganglia, but not by splanchnectomy alone (for review see Goldblatt[1]). In short, it appears probable that either nervous or unknown humoral factors can be concerned in prolonged experimental hypertension.[6, 7, 8, 9, 10]

A candid evaluation of the reported evidence inclines one to the belief that essential and renal hypertension in man are likewise basically due to unknown humoral agents, but that, as in transient hypertension of normal individuals, vasoconstriction of nervous origin may be superimposed periodically or permanently. This squares with various observations: Significant reduction of pressure occurs in many patients as a result of mental and physical rest; blood pressure may be reduced abruptly, but not quite to normal levels, upon compression of the carotid sinus.[11, 12, 9] The peripheral vessels are still capable of dilating in response to heat.[13] The idea of a dual mechanism is also supported by the surgical demonstration that section of efferent vasomotor fibers in the anterior spinal roots or of the splanchnic nerve seems to be beneficial, but may not permanently reduce pressure to normal levels.[14, 15, 16] The evidence that the disturbed nervous mechanism is due to failure of moderator nerves, rather than to disturbance of central origin, does not appear to have much experimental or clinical support. The frequent association of essential hypertension with continued nervous tension, emotional stress and anxiety, as well as the proximity of emotional and hypothalamic vasomotor centers, favors a central origin. It is a priori improbable that nature could easily abrogate all afferent moderator influences, which seems to be necessary to evoke hypertension in animals.

Dynamic Resemblances and Differences.—The zealous search for the humoral and nervous factors concerned in experimental hypertension has temporarily eclipsed careful study of the dynamic changes produced,

so that we can only say that these seem to resemble those of human hypertension. It has been pointed out that experimental hypertension due to severance of moderator nerves is usually accompanied by tachycardia, which is the exception rather than the rule, clinically.[17, 12, 18] That increased cardiac output contributes to elevation of pressure in such instances seems probable. In patients, however, the heart rate and output are generally within normal ranges or even less,[19, 18] and therefore do not appear to be significant factors in the production of hypertension. Such tachycardia is apparently not conspicuous in experimental hypertension of renal origin, although heart rates during the course of developing hypertensions have neither been reported nor analyzed with the detail that dynamic studies merit. Cardiac output and viscosity studies are also not often made in experimental investigations. Indeed, the chief fact established seems to be that systolic and mean pressures are elevated appreciably. Fewer observations on diastolic pressure[20, 21, 22] indicate that it increases rather variably but on the whole less than systolic. The pulse pressure also increases from 30 to 35 per cent. This is much less than is frequently found in patients, in whom increases of 200 per cent or over are not uncommon.[23] To what extent this is caused by the faster heart rates in dogs remains to be determined.

Blood Pressure Measurements in Animals.—It must be admitted frankly that blood pressure readings on animals cannot be accepted with the same degree of surety as in man. This is partly due to the difficulty of utilizing indirect blood pressure recording apparatus on animals and partly to the dilemma of determining when dogs are under basal conditions.

The form and size of the animal's limbs are not designed for application of blood pressure cuffs and despite earnest efforts to overcome these obstacles the author is not convinced on the basis of personal experience that consistent errors are not incurred. Aside from this, pressures in the femoral arteries generally exceed those in the aorta[24, 25, 26] and are more likely to vary independently of aortic pressure[27] than are pressures in the carotid artery. Since we desire evidence regarding pressure variations in the aorta, alterations in femoral pressure cannot be trusted to yield this information. Our best approach is through the use of van Leersum loops of the carotid artery.

With the achievement of direct registration of arterial pressures by the calibrated hypodermic manometers introduced by Hamilton[28, 29, 30] and modified by Gregg,[31] more accurate determinations are possible. At least one such report has been made.[21] However, use of such apparatus involves special training in order to avoid the many pitfalls which beset all optical pressure recording. Hence it can only be recommended to those who are qualified by training and experience in the use of such instruments as well as in the evaluation of the records obtained.

Equipped with such technique, the experimenter is still hampered by the fact that even in so-called "trained" dogs, the blood pressure is much more labile than in human beings. The mere puncture of an artery under local anesthesia or application of pressure cuffs may be sufficient to modify heart rate and blood pressure temporarily. Since the properly trained dog under basal conditions exhibits a considerable degree of sinus arrhythmia, I hereby propose as a criterion of the basal state the existence of some degree of arrhythmia. Its absence in normal dogs probably indicates that they are not sufficiently at ease.

The patient experimenter, however, is merely pushed from one cul-de-sac to another, for the presence of such arrhythmia causes systolic and diastolic pressures to fluctuate from beat to beat. This is indicated to a mild extent in the record of Fig. 1, for which I am indebted to my colleague, Dr. Gregg. The experimenter must therefore choose between reporting the highest and lowest readings for systolic and diastolic pressures or the averages from a complete cycle of arrhythmic beats.

The foregoing considerations indicate some of the difficulties that confront experimenters in determining with exactness the degree of hyper-

Fig. 1.—Pressure variations in carotid artery of normal unanesthetized dog under basal conditions.

tension induced by various procedures. It has added materially to the difficulty of analyzing and comparing the dynamic states in animals with those in man and, as a matter of fact, in differentiating ubiquitous accidental fluctuations from those actually produced by a causative agent. In the interest of further progress we must recognize the unconquered difficulties, as well as applaud the achievements despite their existence.

THE INCREASE IN PERIPHERAL RESISTANCE

Many types of observation indicate that in renal as well as essential hypertension, blood volume, blood viscosity[32, 33, 12] and cardiac output[19, 18] fall within normal ranges; hence the inference based on Poiseuille's law that increased peripheral resistance must necessarily be the primary factor.

The Concept of Central, Collective, and Effective Resistances.—In order to avoid misinterpretations, we must be clear in regard to various conceptions of "vascular resistance." The ejection of blood from the left ventricle is impeded by a central resistance in the root of the aorta. It represents the load of the left ventricle. It has three components: (1) the frictional resistance to flow through the central vessels and distribut-

ing branches, (2) the resistance offered collectively by all the prearterioles and arterioles which regulate the efflux from the arterial tree into the capillaries, and (3) the resistance offered distal to arterioles by changing size and patency of capillaries or by the head of venous pressure beyond them.

(1) The functional resistance between the blood and the walls of the larger arteries normally constitutes 20 to 25 per cent of the total central resistance and remains fairly constant under various conditions, including greater rigidity of the vessels. As Fahr and his associates[34, 35] point out, the resistance involves (a) static changes due to alterations in lumen (e.g., changes due to age, pathologic processes, or to differences in internal pressure) and (b) dynamic changes which vary with the degree of expansion during each systole. Rough physical calculations indicate, however, that extreme static and dynamic changes such as occur in severe arteriosclerosis probably do not cause more than a 2.5 per cent alteration in the total central resistance.

(2) Changes in the caliber of the arterioles, which act as the stopcocks of the arterial tree, constitute the dominant factor affecting the total central resistance. The arteriolar resistance is not the same in all regions of the body; for example, it is high in the leg as compared to the head. Furthermore, these relations may vary greatly during nervous or chemical actions.

The net resistance offered by all the arterioles collectively is generally designated as the peripheral resistance, or better, the effective peripheral resistance. It is obvious that increase in the effective peripheral resistance does not necessarily imply greater impediment to flow through all arterioles and prearterioles. Constriction of vessels with powerful muscular fibers may elevate pressure so much that arterioles like those of the brain or the limbs, containing fewer contractile elements, may be passively expanded and their local resistance actually decreased. Again, active constriction may occur in one region and active dilatation in another, in which event the change in effective peripheral resistance would be a resultant of two contrary changes. The physiologic principle emerges that it becomes hazardous to draw conclusions regarding changes in the effective peripheral resistance from observations of a single organ or a limb.

(3) Active changes in the size of capillaries and the pressure on the venous side of the capillaries may exert an additional influence on peripheral resistance, e.g., in shock. It is, however, the writer's impression that its dynamic importance was exaggerated during the years of enthusiastic study of capillary actions. Certainly there is little evidence that capillary or venous resistances are important factors affecting the central resistance during hypertension except when venous congestion supervenes during ultimate decompensation.

Such considerations allow us to look upon changes in the effective peripheral resistance as essentially synonymous with alterations in central aortic resistance.

The Magnitude of Increase in Effective Peripheral Resistance and Its Relation to Blood Pressure.—The generalization that the peripheral arterioles are chiefly involved both in renal and essential hypertension is substantiated by the clinical observations that the greatest drop in pressure still occurs in the arterioles of limbs[36, 37] and that the blood flow through the arm or hand is within normal limits despite the higher brachial pressures.[12, 13]

Such samplings of local peripheral resistances of course give no information as to the collective or effective resistance to flow from the

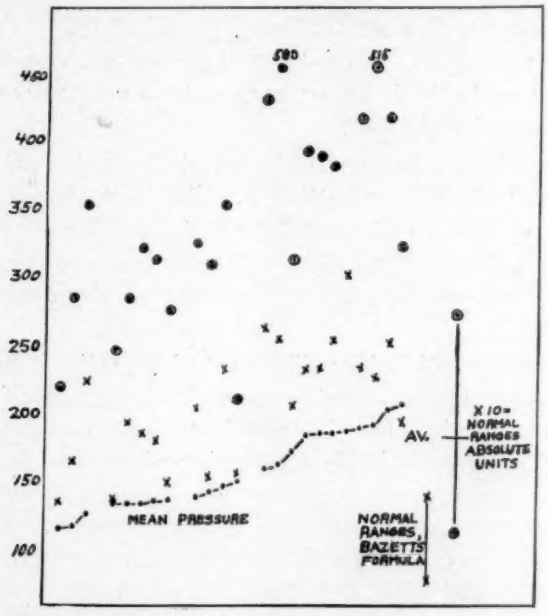


Fig. 2.—Plots showing relation in patients with hypertension of mean pressure (lower curve) to effective resistance calculated in absolute units (⊙) and in Bazett units (×). Ordinate values for absolute units should be ×10.

arterial tree. Fortunately this can also be calculated either in absolute or arbitrary units by use of several formulae,[38, 39, 40] although to my knowledge no effort has previously been made either to demonstrate the existence of an augmented collective resistance in hypertension or to gauge the extent of the increase by such a procedure.

Using the convenient equation, $R = 3\frac{Pm}{Vt/A}$, in which Pm = mean pressure in mm. Hg, and Vt/A = the cardiac index, Bazett, Cotton, et al.,[38] by refined technique, calculated arbitrary values ranging from 79 to 138 for normal subjects. Recalculating their results by using one-half systolic plus diastolic pressure for mean pressure causes no significant

difference. The values range from 80 to 139 arbitrary units. If in a similar manner we calculate R for hypertensives from data published by Soma Weiss and associates,[18] it can readily be seen from Fig. 2 that all of these cases show some augmentation of effective resistance. While, as a rule, it increases with mean pressure, this is by no means invariably true. Some patients with very extreme elevation of pressure have no greater effective peripheral resistance than others with very moderate hypertension. This suggests that augmented peripheral resistance is not the only coefficient in clinical hypertension.

Similar conclusions can be drawn when effective resistance is calculated without regard to surface area, using the formula $R = \frac{Pm \times 1332}{Vt} = \frac{\text{dynes} \cdot \text{sec.}}{\text{cm.}^5}$, in which Vt denotes cardiac output per second. Plots of such values are shown in the upper graphs of Fig. 2, in comparison with the extreme and mean values in normal subjects reported by Böger and Wezler.[39] A more extended use of such calculations in clinical practice might easily lead to a better subdivision of cases than now exists, and its extension to experimental hypertension would offer better comparisons with human forms than do studies of blood pressures alone.

While considering the topic of peripheral resistance and its calculation, we may allude briefly to the question whether concurrent diminution of vascular distensibility so commonly found in hypertension might affect the effective resistance. The possibility exists that the altered form of the pressure wave reaching the peripheral arteries and perhaps the arteriolar orifices could modify the net efflux and hence the calculated peripheral resistance. We have recently studied this question by the aid of circulation models in which a mechanical resistance was kept fixed while the elasticity of the system was quickly diminished. In such experiments, illustrated by data in Fig. 2, calculation of the resistance in absolute units, as above, showed that these figures change very insignificantly as a result of a great increase in rigidity of the artificial aorta, regardless of whether the peripheral resistance was large or small when rigidity was created.

Territorial Distribution of the Augmented Resistance.—Physiologic experiments beginning with the studies of Ludwig and von Cyon[41] and the early studies of Bayliss and Bradford[42] have demonstrated that an intensive constriction of smaller vessels must occur in normal animals in the splanchnic area in order to cause an elevation of pressure equal to that found in hypertension.

The following facts seem to have been demonstrated: (1) Excitation of nerves to a limb or of the nerve roots between the second thoracic and fourth lumbar causes no rise of mean pressure in animals, provided the splanchnic nerves are cut during stimulation of the lower nerves. (2) Stimulation of the splanchnic nerves produces a great elevation of pressure even after removal of the adrenal glands. (3) In atropinized animals, under mild artificial respiration, similar in-

creases in blood pressure accompanied by decrease in the volume of abdominal organs and increase in that of the limbs can be produced by excitation of pressor fibers in the sciatic and vagus nerves. These effects are greatly reduced or absent after section of the splanchnic nerves. (5) Ligation of the main branches of the aortic arch, together with the common iliacs, does not significantly alter the calculated effective resistance (our observations). (6) Compression of the aorta progressively upward as a rule causes no pressure elevation until a clamp is applied above the origin of the superior mesenteric vessels.

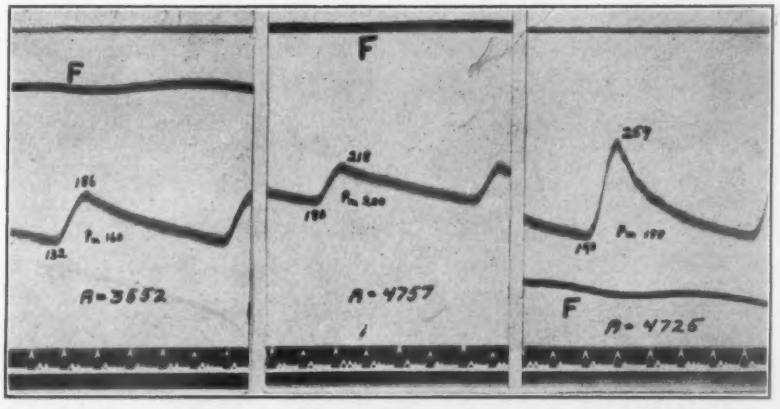
These and other experiments lead to the reasonable inference that if arteriolar constriction is the primary and chief cause of human and experimental hypertension, the splanchnic area must be dominantly involved. This does not preclude simultaneous constriction of vessels in other organs or in the limbs, for which evidence has apparently been produced, among others by Pickering[12] and by Prinzmetal and Wilson.[13] But any thesis that their contraction can add significantly to elevation of general blood pressure lacks proof. It is conceivable that the greater relative mass of human limbs might make a difference. But nowhere in the literature have I found evidence that dilatation of arm vessels following nerve anesthesia or application of heat reduces hypertension significantly. On the contrary, it is well known that complete deprivation of the circulation to limbs in organic or spastic types of vascular disease, or total loss of several limbs, does not cause even a moderate hypertension.

The Nature of the Arteriolar Resistance.—Successive observation by Gull and Sutton (1872), Jores (1904), Evans (1920), Fahr (1922), and others that thickening of the walls of minute vessels occurs led to the view that generalized changes in the intima and media of smaller vessels are responsible for the augmented peripheral resistance. However, attention has been directed repeatedly to the fact that the lesions are more often limited to a few organs, the kidney, spleen, pancreas, liver, brain, and retina being involved in order of frequency and severity. With the detection of similar arteriolar changes in biopsies of skeletal muscle[43, 44] it seemed probable for a time that organic changes might be more general than was then believed. Subsequent studies[45, 46] seem to have shown that such preparations do not necessarily give information regarding changes in vessels of the internal organs. Furthermore, it is debatable whether the lumina are actually decreased during life.

Lacking a sound morphologic basis for an augmented resistance the view naturally shifted to the postulate that a sustained functional contraction, unwisely designated vascular spasm, results through the action of humoral or nervous agents. No one, however, has submitted good visual or photographic proof of the occurrence of such constriction except in the retinal vessels. Microscopic studies of blood vessels in the skin and nail bed, originally undertaken by Lombard,[47] have not proved as helpful as was hoped. Our evidence is entirely indirect, i.e., based on the calculation of effective resistance.

THE ROLE OF LARGER ARTERIES IN HYPERTENSION

Physical Importance of Arterial Elasticity.—By virtue of their large caliber and highly elastic walls, the aorta and its immediate branches act like the compression chamber (Windkessel) of a fire engine in that they buffer variations in pressure and flow.[48] Experiments on circulation models indicate that when peripheral resistance and output remain the same, an extreme increase in rigidity of larger vessels acts chiefly to redistribute systolic and diastolic efflux from the system, thereby increasing systolic, and decreasing diastolic pressure. Mean pressure either remains unchanged or may rise or fall a trifle (Fig. 3). Fahr, Davis, and Spittler[34, 35] found similar changes when the naturally beating heart constitutes the pump. The conclusion seems to be clear that a rise of both pressures with significant increase in the mean pressure, such as occurs in hypertension, can occur only when peripheral resistance is augmented in



A. B. C.

Fig. 3.—Three pressure pulses recorded optically from circulation model. *A*, *B*, Effect of increasing peripheral resistance on pulse pressure and calculated effective resistance. *C*, Effects on pulse pressure, mean pressure, and calculated effective resistance of superimposing rigidity of central vessels, while actual peripheral resistance remains the same in *B*. Records *F* indicate peripheral volume flow. Compensated in *B*. Note reduction in *C* as result of arteriosclerosis and fall of mean pressure.

addition. This does not signify, however, that provided peripheral resistance is increased, diminished elasticity of the central vessels may not accentuate the height to which systolic pressure is elevated by the force of the ventricular contractions. This is clearly shown by comparing curves A, B, and C of Fig. 3. An increase in effective resistance from 3,552 to 4,757 absolute units decreased the pulse pressure and increased the mean pressure from 160 to 200 mm. Hg. With essentially the same peripheral resistance of 4,725 absolute units, superposition of a less elastic state of arteries increased systolic and reduced diastolic pressures.

It has often been suspected that diminished extensibility of the central vessels in this way contributes to the elevation of systolic pressure in many cases of hypertension. Furthermore, a grave suspicion exists that

this means not merely a normal decrease in expansion of vessels such as occurs at higher internal pressure, but rather that some functional, physical, or structural alteration, perhaps in the nature of premature aging, is concerned. However, it has proved difficult to obtain good tangible proof for its existence.

The Effects of Age on the Structure and Physical Characteristics of the Aorta.—Although arteriosclerotic changes exist in the aorta and palpable vessels in some individuals with hypertension, it is generally conceded that severe hypertension occurs without its presence. In addition, and quite apart from such obvious pathologic changes, it is well known that the aorta of normal individuals undergoes certain changes with age. The lumen begins to increase at puberty and by the age of forty years may be even greater than the sum of the cross sections of its branches.[38, 49] Coincidentally, the walls gradually become thicker, their elastic tissue decreases, the collagenous fibers seem to increase, and their distensibility with increasing pressures is reduced according to well established rules.[50-54] The trend is indicated by the curves of Fig. 6, which will be discussed later.

Since the volume-elasticity coefficient, $\frac{dp}{dv}V$, which expresses the degree of rigidity, depends on the ratio of pressure to volume increase, $\frac{dp}{dv}$, as well as on the diastolic volume, V, changes in size and distensibility tend to neutralize each other during the process of normal aging, as far as the central "compression chamber" function is concerned. If, however, changes in size and elasticity are not thus adjusted, the buffering function of the central reservoir suffers. But studies of human vessels by microscopic or physical methods are not numerous enough to warrant deductions as to the existence of such maladjustments of distensibility with respect to size during hypertension in different age groups, and even if such relations were established with meticulous care on autopsy material the suspicion would still remain that the observations might not apply to the vessels during life.

The possibilities also exist that physical changes in elasticity may precede evident histologic alterations, or that functional variations in elasticity may occur during life as a result of altered muscular action. Hochrein and Lauterbach[55] presented a few cases which seem to support the first of these possibilities.

The Role of Muscular Action.—How muscular contraction affects the volume-elasticity coefficient in the aorta and its branches remains debatable. In distributing arteries, contraction of circularly disposed, spindle-shaped muscle fibers reduces the size (V) and increases the ratio, $\frac{dp}{dv}$, particularly at lower ranges of pressure. The effects in the aorta and its immediate branches are debatable. Indeed, the arrangement and purpose of the muscular elements remains an enigma. The

muscle cells are sparse and no longer spindle-shaped. They assume broad, short, irregular forms; sometimes they are serrated, stellate cells, the branches of which perhaps fuse, forming a syncitium.[56] I have always doubted whether such cells can have any significant influence on vessel size or elasticity. Hürthle[57] presented results which he interprets as indicating that the aorta participates actively in forcing blood into the iliac branches. Bazett, Scott, et al.,[38] on the basis of pulse velocity studies, believe that their contraction decreases the elasticity of the aorta significantly. According to Benninghoff,[56] the muscle fibers are arranged radially or tangentially and are so joined to wavy elastic fibers that in contracting they straighten these elements and reduce their tension. If this is true, muscular contraction should increase the lumen slightly and the elasticity significantly.

We may hasten to add that experimental evidence of a routine sort does not seem to support this pretty theory. Rings of large arteries, as well as of smaller muscular vessels, have repeatedly been placed in oxygenated Locke's solution and their reactions tested. Under proper conditions they respond by decrease in diameter upon direct mechanical, electrical, chemical or thermal stimulation.[58, 59] The subject, however, deserves further experimental study of a more direct sort.

Pulse Velocity Studies as Criteria of Elasticity Changes.—Since the velocity of pulse wave transmission is related to the square root of vascular distensibility, as expressed by the formulae of Moens,[60] O. Frank,[61] Bramwell and Hill,[62] and others, the uninitiated are likely to assume that abnormal states of elasticity in patients with hypertension should be easily detectable by this means. Time is lacking to deal adequately with the numerous complications and hazards that attend use of the method. Laborious researches have shown that the pulse velocity is less in central than in peripheral vessels, that it increases with age, that it depends on the pressure within the vessels, and, in peripheral distributing vessels, at least, also on the state of muscular contraction. But still no uniformity of opinion exists as to whether the propagation rate in any set of vessels is faster in cases of hypertension when correlated with pulse velocities of normal subjects of similar ages, similar pressures, etc.[63]

In 1932 I reviewed[23] the advantages and also some of the errors that may enter into an ingenious method proposed by Bramwell and Hill,[62] viz., that of exerting variable counter pressures by means of a blood pressure cuff and measuring pulse velocities at different *effective internal pressures.* Those who have used this procedure[63] have been unable to establish significant differences between patients and normal subjects.

Attention may now be directed briefly to the recent proposal by German investigators[39, 55, 64] to establish quotients of $\frac{\text{peripheral velocity}}{\text{central velocity}}$, a procedure which has the merit of evaluating changes in different vessels at the same time, in the same person. However, variations with age and blood pressure still need to be established through correlation studies. A

limited number of normal quotients at different ages, together with those from eleven cases of hypertension analyzed by Böger and Wezler,[39] are incorporated in the lower graph of Fig. 4. From such data, which appear altogether too few in number, and from changes which are too small, they conclude that the quotient increases in young individuals with hypertension but decreases in older persons with hypertension. This and other studies lead them to support Benninghoff's conception that muscular contraction increases the distensibility of larger vessels and that abrogation of such contraction decreases their distensibility in hypertension. I have similarly calculated and plotted quotients from the much larger number of normal subjects and patients with hypertension recently studied by Haynes, Ellis, and Weiss.[63] As indicated by the upper

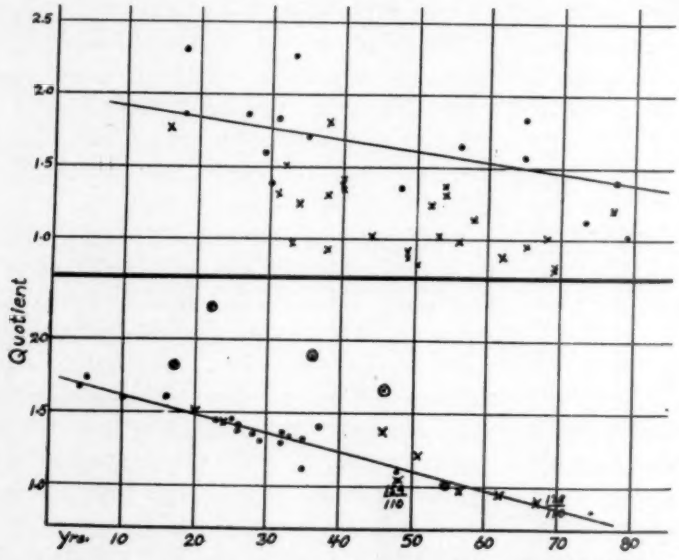


Fig. 4.—Two sets of plots showing quotients, $\frac{\text{central pulse velocity}}{\text{peripheral pulse velocity}}$, in normal subjects (dots), and in subjects with hypertension (× and ⊙). Upper series from data of Haynes, Ellis, and Weiss. Lower series from data of Böger, Wezler, and Hochrein. Note general tendency of normal quotient to decrease with age. Ordinates = quotients; abscissae = age. Discussion in text.

plot of Fig. 4, the quotients of patients with hypertension at all ages seem to be lower than normal. If any conclusion is permissible, it would be that the elasticity of central vessels is reduced rather more than that of the limb vessels.

It is hazardous, however, to place too great confidence in these, or in other types of pulse velocity study, for while significant improvements have been made in the technical methods for recording pulses, the problem of accurate measurement of actual arterial lengths has not been conquered. If we take cognizance of the diversified architecture of the arterial tree in different subjects[65] and the variations in vessel lengths due to posture, tortuosity, etc., it becomes apparent that the small differ-

ences in velocity occasioned by considerable changes in elasticity may be obscured or apparently exaggerated through imperfect measurement of distances.

The Augmented Pulse Pressure and Altered Pressure Pulse in Clinical Hypertension.—The term *pulse pressure*[66] refers to the difference between systolic and diastolic pressure. As determined by clinical methods this gives an index of the extreme variations of pressure. The term *pressure pulse*[67] was introduced to incorporate all the pressure variations occurring from moment to moment during the cardiac cycle. It is the pressure curve recorded by calibrated optical manometers inserted into arteries. A subclavian pulse recorded in man by use of optical methods gives the form of these pressure variations without ordinate values. The

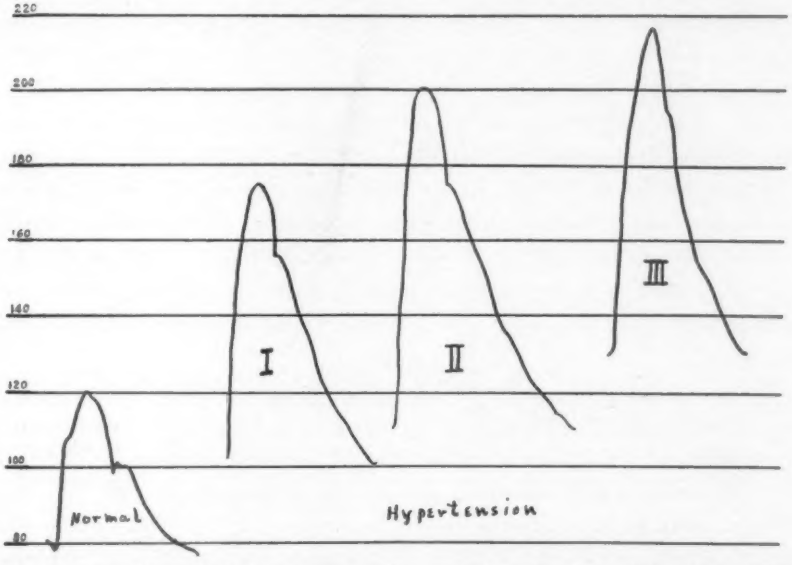


Fig. 5.—Four transcribed pressure pulse curves reduced to the same ordinate values by use of Green's coordirectograph. First curve from normal medical student, for comparison. I, From patient with essential hypertension, aged 37 years; II, from patient with nephrosclerosis (aged 59 years); III, from patient with general arteriosclerosis (aged 61 years).

latter can be supplied, with not too great an error to be useful, if the readings of systolic and diastolic brachial pressures are used as values for the highest and lowest points of such a curve and equal divisions are made between these ordinates. When this is done in the case of hypertension and records are redrawn with equal ordinates, curves such as are reproduced in Fig. 5 are obtained. The first is from a normal medical student, the other three from cases of hypertension recently studied at the University Hospitals.

In 1932[23] I concluded that the form of such pressure pulses and the enormous increase in their amplitude over the normal could only be explained by assuming that the elasticity of the larger vessels is decreased. The evidence upon which this conclusion was based may briefly be re-

stated: (1) Pulse pressures declined with increasing resistance—up to pressures of 200 mm. Hg—when an isolated dog's aorta was perfused with rhythmic variations of pressure, whereas it increased after the aorta had been gradually hardened by formalin. (2) The form of the pressure pulse obtained in hypertension (Fig. 5), with its abrupt rise, peaked summit, and rapid decline, resembled that from an aorta hardened by formalin perfusion. (3) The clinical evidence, which has been since supported by data obtained by better methods, suggests that increased systolic discharge is not a probable factor.[18, 19]

Soma Weiss and his co-workers,[18] who have diligently studied patients with hypertension for many years, were recently forced to the same conclusion, despite their failure to find changes in velocity that deviated from the normal. Volhard[68] has long insisted that it is the larger vessels which are predominantly involved in so-called "red hypertension." Two facts have compelled me to reconsider these opinions: (1) A number of friends whose opinion I respect have suggested that at pressures variously placed between 80 and 140 mm. Hg the distensibility even of youthful arteries may diminish so much that larger pulse pressures may be expected with increasing peripheral resistance. If this be the case one need not assume an additional decrease in rigidity to explain the large pulse pressures in hypertension. (2) I have reported[23] that reflex vasoconstriction in the dog does not decrease pulse pressure, but uniformly increases it.

(a) Circulation Model Experiments.—Changes in elasticity resembling those found in man as a result of aging or pathologic processes[50-54] cannot be reproduced easily in animals, and if reproducible would certainly introduce conflicting reactions in cardiac rate and output. Therefore physical tests were again made on circulation models. In these, cardiac rate and output can be kept constant and the interacting effects of changes in peripheral resistance and distensibility can be studied. The results, reported in detail elsewhere,[69] can be quickly surveyed by the aid of a single graph (Fig. 6). The curved lines represent a selected series of volume-pressure relations at different pressure levels which could easily be reproduced in the machine and were determined each time. Curve *A* is that of an ideally expanding system in which the relations $\frac{dp}{dv}$ are linear. Curve *B* likewise shows a linear proportionality up to 100 or 120 mm. Hg, but beyond this distensibility decreases progressively. Such a curve is fairly comparable to that obtained in young adults. Curve *C* shows a diminution of distensibility at pressures around 60 to 80 mm. Hg; and approximate curves obtained from human aortas during middle adult life, curve *D*, show great reduction of distensibility at very low pressures and a total expansion that is never very great. Curves C^1 and D^1 illustrate the changes when the distensibility is the

same as in *C* and *D*, but the capacities of the system at 20 mm. Hg internal pressure were 35 and 70 per cent larger with respect to the systolic discharge.

The effects of increasing the peripheral resistance on pulse pressure under these different conditions were recorded by a calibrated optical manometer, but for convenience they are directly superimposed on the volume-elasticity curves. For original curves see Wiggers.[69]

In a system in which the volume-elasticity curve is a straight line (curve *A*), pulse pressure decreases to the very limit of the system (beats 1 to 5). When the distensibility begins a progressive decrease at about 120 mm. Hg, as in curve *B*, the pulse pressure decreases uniformly except

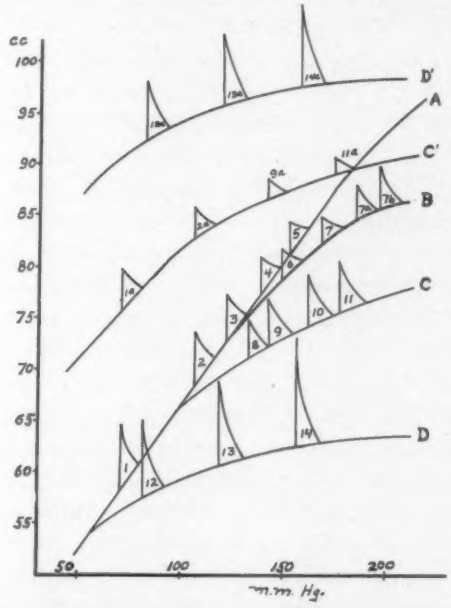


Fig. 6.—Series of graphs illustrating volume-elasticity coefficients at different pressures (abscissae) and the essential changes in pulse pressure found in a circulation model under these conditions. Discussion in text.

at the very uppermost ranges, where it may become larger again (beats 7a, 7b), but never exceeds that of beats at lower pressures (e.g., beats 1, 2).

If, as in curve *C*, the distensibility begins to diminish at about 85 mm. Hg and thereafter decreases rather more, the pulse pressure is still reduced until the pressure reaches about 120 mm. At higher pressures it increases rapidly, but at very high pressures, the beats (10 and 11) are not generally larger than beat 1, though they are larger than beats 2 or 3. This effect is annulled by a 35 per cent increase in the initial volume, as shown in curve C^1. If, as post-mortem studies indicate, the size of the aorta also increases with age, only a reduction in pulse pressure could be anticipated in individuals during middle adult life. If, finally, expan-

sion of the arterial system is limited from the start and the extensibility curve shades off at lower levels, as in old age (curve *D*), the pulse pressure increases from the start and becomes progressively larger. The magnitude of the increase is reduced by a 70 per cent increase in vascular volume (curve D^1). This is shown by comparison of beats 12, 13, and 14 with 12a, 13a, and 14a.

If the facts thus established are applicable to man, they suggest (1) that the importance of diminishing elasticity with increasing pressure as a factor which determines directional changes in pulse pressure has been greatly overestimated, and (2) that granting an unaltered heart rate and systolic discharge, such large pulse pressures as are found in patients with hypertension (Fig. 5) cannot occur except in very old people without assuming an additional rigidity.

(b) Studies on Animals.—I would be among the last to claim that observations on such artificial circulation schemes can be regarded as the final court in deciding the operation of mechanisms in the body. They do, however, allow a first approximation toward guiding principles which can then be further tested on living animals. Fortunately, the changes in pulse pressure observed in persistent experimental and human hypertension can also be produced acutely in animal experiments. This permits the problem to be returned to physiology laboratories for that intimate analysis of dynamic factors which is only possible in acute experiments.

Several types of experiments are in progress which throw further light on the situation in the body. In a first series of experiments the aortas of dogs which had recently died or were in the process of dying were left in situ and perfused with the pump of the circulation model. In this way the effects of increasing peripheral resistance could be tested on the aorta under natural conditions, for the possibility has been suggested[51] that since the aorta in the body is bound down by the adventitia it may be less expansile than tests on removed sections indicate. To obviate ligation of numerous branches, a very thin rubber "inner tube" was passed down the ascending aorta to the iliac branches. To our astonishment, volume-elasticity curves obtained under such conditions in ten street dogs resembled those of *A* in Fig. 6. Diminishing distensibility first became evident at pressures near 200 mm. Hg. It is, therefore, not surprising that a progressive increase in peripheral resistance caused a continuing decrease in pulse pressure. It may be suggested that curves resembling those of *B* and *C* obtained in post-mortem studies of the human aorta may have resulted from post-mortem contraction or even a state of rigor mortis in vessels examined some time after death.

In a second series of experiments, we further studied the possible causes of the increase in pulse pressure that occurs with pronounced vasoconstriction in anesthetized dogs. Repeated tests showed clearly that systolic discharge increases immediately with the rise in blood pressure

and becomes steadily greater. The chief cause seems to be an augmentation of venous return due to constriction of the spleen, but the effects of systolic retention of blood and possible increase in epinephrine output during the height of the pressure increase doubtless contribute. Such experiments indicate that the increasing pulse pressure could be fully explained by the greater systolic output.

Since it is possible, however, that the remarkable degree of elasticity exhibited by the aortas of dogs which were in the process of dying or had just died was due to an immediate loss of tonus and may not represent conditions in the living dog, additional tests were made, in association with Dr. Wegria, to ascertain the relation between diastolic and pulse pressures and the degree of expansion at different pressure levels. The latter was obtained by applying a tiny arteriograph to various portions of the descending thoracic aorta, intact within its supporting sheath and with its natural nerve and blood supply untouched. While the investigations are not completed, the results suggest that as a rule a mechanical increase in resistance caused by compressing the aorta just above the diaphragm produces corresponding changes in pressure variations and wall expansion. However, following elevations of pressure produced by reflex vasoconstriction, adrenalin, and pitressin, the expansion is progressively reduced. It therefore appears probable that changes in the capacity and elasticity coefficients of the aorta do participate in the augmentations of pulse pressure obtained experimentally and perhaps also in experimental and human hypertension.

The Peripheral Flow in Hypertension.—If pressure pulses of patients are given ordinate values as suggested, the curves can be integrated by measuring the surface areas beneath a whole curve, or portions of it, and the mean pressure thus calculated by dividing by the horizontal distance. When this is done, as in Fig. 7, it is found that the mean pressure for the whole cycle (M) is elevated and bears a variable relationship to systolic and diastolic pressure. In contrast to normal curves, the bottom of the incisura (I, second curve), marking the moment that the semilunar valves come into apposition, always lies much above the mean pressure level in hypertension, whereas it very nearly coincides with it in normal individuals.

The mean pressures during periods of systole and diastole can be calculated in a similar way and are denoted by rectangles (P_{ms}, P_{md}) in Fig. 7. Such a geometric analysis of calibrated curves clearly shows that mean systolic pressure is increased and mean diastolic pressure is decreased. Since these values represent the average forces which drive blood from the aorta and perhaps its large branches during systole and diastole, it becomes obvious that systolic runoff increases and diastolic efflux decreases.

Recent dynamic studies[69] also indicate that as long as the peripheral distributing arteries remain distensible they serve as a buffer which prevents significant variations of flow through the arterioles and capillaries.

In other words, while the distributing vessels receive more blood during systole and less during diastole, the runoff from the arterioles remains fairly constant throughout the cycle. If, however, the peripheral vessels are also involved, the peripheral buffer chamber is lost and the flow through capillaries becomes intermittent. In this manner a capillary pulse can develop despite the existence of marked arteriolar constriction. The idea that capillary pulsations in hypertension and aortic insufficiency cannot occur except through vasodilatation is an incongruity in the field of cardiodynamics. However, whereas capillary pulsations due to vasodilatation occur on account of a systolic acceleration of flow, those associated with large pulse pressure and increased peripheral resistance are due to a periodic reduction of flow later in diastole, i.e., when arterial pressures sink to low levels.

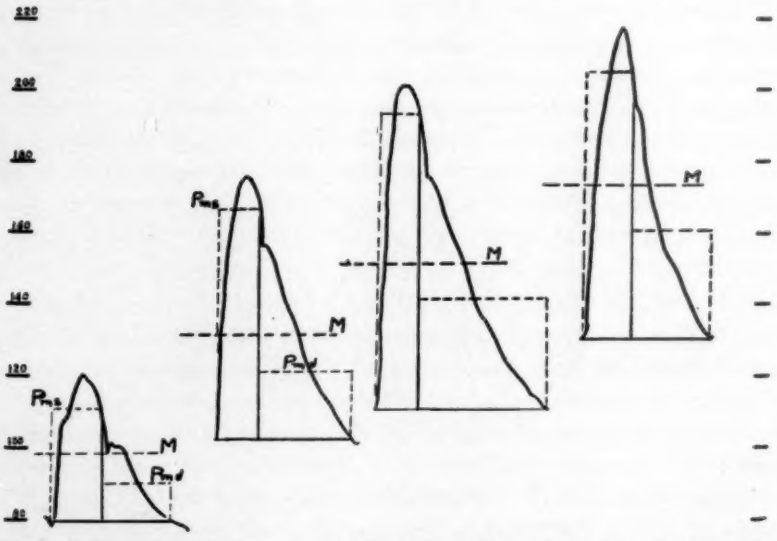


Fig. 7.—Pressure pulses from same patients as those in Fig. 5 showing calculation by integration of values for mean pressure of cycle *(M)* and mean pressures during systole and diastole (indicated by rectangles *Pms and Pmd*). Discussion in text.

CARDIODYNAMICS

The effects of hypertension upon the dynamics of the left ventricle are determined chiefly by the increased load. In acute experiments the systolic output, as determined in various ways, seems to increase somewhat or at least is not diminished as a result of increased peripheral vasoconstriction or aortic compression.[70, 71, 72] By use of a heart-lung preparation and cardiac plethysmograph the mechanism was partially elucidated by Starling, et al.,[70] and by Straub.[73] During the first few beats following a sudden increase in aortic pressure systolic discharge decreases, thereby leaving a small residual volume within the left ventricle. Since normal volumes flow from the left auricle into the left ventricle during

each diastole, the diastolic volume increases, the muscle fibers are stretched, and in consequence the left ventricle contracts more vigorously, thus restoring the stroke volumes to or slightly above normal. We have recently found that translocation of blood from abdominal organs, particularly the spleen, also occurs. This causes an increase in venous return to the heart.

Such a greater systolic output must involve a change either in the velocity or duration of ejection. Starling and his associates emphasized prolongation of ejection. The question was properly raised whether such results are also applicable to the circulation in the body, for the venous pressure is not easily kept constant in heart-lung preparations, owing to the tremendous increase in coronary flow. The same holds good for pulmonary pressures.[74] Katz and I[75] demonstrated, however, that similar reactions do occur in the intact circulation when neither venous pressures nor pulmonary pressures alter. By means of optically recorded aortic pressure and ventricular volume curves we showed that the ejection period tended to be reduced, but that the velocity of ejection increased. How this comes about can be analyzed better by registration of ventricular pressure curves, for we are confronted with a cardiodynamic situation in which the left ventricle contracts against a larger afterload and is stretched during diastole, whereas the right ventricle continues to operate under approximately normal conditions in the body. These details have been analyzed elsewhere.[67]

Similar reactions apparently occur in human hypertension, for evidence shows on the one hand that systolic discharge is essentially of normal magnitude,[18, 19] whereas total systole and the ejection phase are generally increased slightly as long as the heart remains competent.[76, 77] Evidence is at variance as to whether duration of isometric contraction increases or decreases slightly.[76, 78]

Cardiac Work.—It is easy to prove by the application of simple equations ($W = QR + \frac{WV^2}{2g}$, Evans[79]) in which changes in kinetic energy of flow (second factor) are disregarded, that the work of the left ventricle is augmented. The probable increase in the case of the human heart when pressures rise from 120/80 to 240/130 mm. Hg was estimated as about 95 per cent by Fahr,[80] who used the potential energy factor (first) of the equation, $W = \begin{cases} Ps \\ Pdv \\ Pd \end{cases} + \frac{SV^2}{2g}$, and the distensibility curve of mean normal arteries given by Bramwell and Hill.[62] Similar conclusions were reached in case of experimental animals by Straub,[81] who constructed geometric work diagrams from simultaneous pressure and volume changes of the heart. Both agree that the increase in work is nearly proportional to the elevation of systolic pressure and relatively much greater than the elevation of mean or diastolic pressure.

These calculations, in fact, fall short of the actual increase in left ventricular work since the considerable increase in velocity during systolic ejection is not taken into account, a point to which many investigators have appropriately called attention.

The Efficiency of Beat.—The efficiency of cardiac muscle may be expressed as the ratio, $\frac{\text{total energy expenditure}}{\text{work in kilogram-meters}}$. In the heart-lung preparation the latter can be calculated from oxygen consumption, and this is readily translated into kilogram-meters. In this way the normal efficiency has been estimated at 20 to 28 per cent, under varying conditions, by Evans.[79] It seems to have been definitely established that not only is the oxygen consumption increased almost in proportion to the elevation of arterial pressure, but that the efficiency of contraction is slightly improved.[19, 82] Evans and his co-workers[83] suggest that this increased energy may be derived from oxidation of lactic acid, and that the latter may be partly responsible for the increased efficiency.

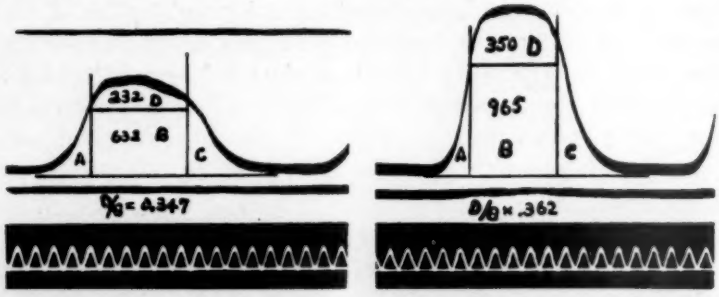


Fig. 8.—Two curves showing the effect of increasing arterial resistance on intraventricular pressure of dog, and the method of Wiggers and Katz for comparing the economy of effort as ratio, $\frac{\text{area } D}{\text{area } B}$. Note that no significant differences in D/B ratio exist. Discussion in text.

Unfortunately, such estimates of efficiency are not applicable to the intact animal and even less to man. Hence, we know almost nothing as to how economically the heart operates when hypertension is maintained, and whether subsequent development of hypertrophy improves or impairs the efficiency of its beat.

With the probability that a relationship exists between the efficiency of contraction and the economy with which mechanical energy developed is utilized, Katz and I[84] compared the static and dynamic efforts of the heart beat during ejection by analysis of tension-time relations in ventricular pressure curves. The idea may be expressed by the following analogy:

Suppose an individual desires to throw the contents of a pail with some force over a high wall. Such an act would require an initial and sustained energy expenditure in raising the pail above the level of the

wall and of holding it at this height (static effort), plus additional energy required to throw its contents over the wall (dynamic effort). Similarly the heart expends energy in the static effort of elevating pressures to aortic diastolic levels and of maintaining such a level during ejection. The pressure energy developed over and above this during ejection is immediately utilized to overcome resistance and maintain systolic flow, and the remainder becomes converted into energy of flow during diastole, i.e., potentially it represents dynamic effort.

The left intraventricular pressure curve is enlarged, copied, and divided into four areas labeled *A*, *B*, *C*, and *D*. This is illustrated on

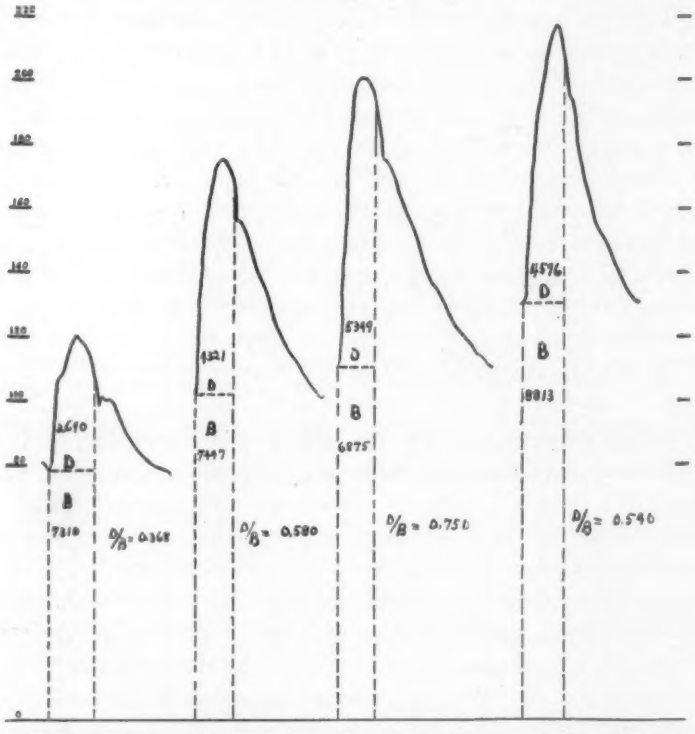


Fig. 9.—Pressure pulses from same patients as those of Fig. 5 and 7, illustrating method for calculating economy of effort on patients as the ratio, *D/B*. Note the great improvement in utilization of the energy released, as denoted by increase in ratio, *D/B*.

original curves in Fig. 8. Areas *A* and *C*, measured with a planimeter, represent the static efforts required during isometric contraction and relaxation, respectively. Areas *B* and *D*, marked off under that portion of the curve representing systolic ejection, are respectively considered to be indexes of the static and dynamic efforts during ejection, because area *B* represents the pressure energy required to sustain the blood column at a diastolic level, and area *D* represents the energy which is convertible into energy of flow. Since changes in the capacities which occur

from moment to moment in the ventricle affect both areas equally and simultaneously, the ratio $\frac{\text{area } D}{\text{area } B}$ expressed the economy of effort.

The two curves reproduced in Fig. 8 show at a glance that as soon as the heart compensates as a result of a greater diastolic size and initial tension (i.e., during the second stage described above), area *D* increases relatively more than area *B*. Occasionally this restores the quotient to normal, hence the deleterious effects of an increased afterload are neutralized. The heart never overcompensates, in the sense that the quotient becomes greater than normal.

Such reactions on animals are merely indicative of what may occur in man; they do not take into account unknown adaptive mechanisms that can be introduced in persistent clinical hypertension. With the hope of comparing the economy of effort in patients with hypertension and normal subjects, Dr. Wright and Dr. Hallaran are engaged in an attempt to apply the method clinically. The basis of comparison consists in obtaining good subclavian arterial pulses and considering the systolic and diastolic pressures obtained from the brachial artery as the ordinate values of such curves. Since these curves may be regarded as the summits of intraventricular pressures, the areas *D* and *B* (Fig. 9) can be determined by dropping perpendiculars to an arbitrary zero level. Results in process of publication leave no doubt that, as shown in these curves, the efficiency with which the ventricle utilizes the energy is far above normal in human hypertension.

The Cardiac Reserve.—While the efficiency of beats in patients with hypertension seems to be increased, we must not lose sight of the fact that the hearts of such patients are continually working nearer their limits of cardiac reserve. If volume curves of the ventricles are recorded in experimental animals while the venous return is progressively increased during acute hypertension (Fig. 10), the records show that the ventricles dilate progressively and that the systolic discharge increases up to a certain point (*C*), but beyond this decreases. This illustrates in a simple way the reactions to increased stretch, regardless of how it is produced, including such conditions as hypertension, aortic lesions, etc. The region of the curve *BC* represents the reactions termed compensation; the regions *CD*, those variously designated as cardiac failure or decompensation.

Now since the normal heart operates in a region to the left of *A*, any further increase in diastolic distention through augmented venous return, such as is produced by muscular exercise, for example, causes a compensatory increase in systolic discharge (*AC*). If, however, as in severe valvular lesions or hypertension, the heart is already operating in the region *AB*, a similar or even smaller increase in venous return, due to exercise, at once shifts the reactions of the ventricles to the areas *BD;* in other words, temporary decompensation occurs. This explains

the limited capacity of such individuals for exercise and the development of an effort syndrome upon exertion. Another way to express these thoughts is that normally the shift of cardiac reactions upon exertion to *AB* or *BC* brings the cardiac reserve power into action; but in hypertension the ventricles are already operating in the field of cardiac reserve, *BC*, and further dilatation shifts their reactions beyond this field, i.e., into area *CD*. Such analysis ought to give a clearer meaning to such commonly used terms as cardiac reserve, compensation, and decompensation.

The Coronary Flow.—Since, during hypertension, the total energy exchange, as well as the work of the ventricle, increases very nearly as the systolic pressure, provision ought to exist for a correspondingly aug-

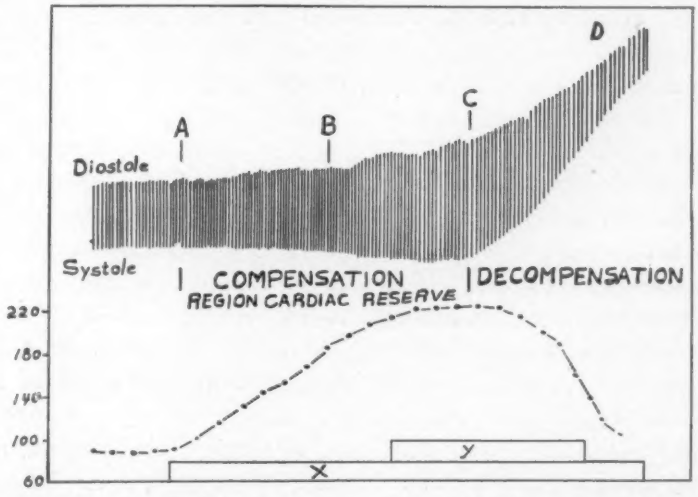


Fig. 10.—Plot showing changes in upper curve in diastolic and systolic volumes and in systolic discharge and in lower curves, changes in mean pressure during stimulation of pressor fibers in vagus nerve, *(X-X)*, and during added infusion of 300 c.c. saline *(Y)*. Discussion of phenomena of cardiac reserve, compensation, and decompensation in text.

mented coronary flow. Indeed, sclerosis of the coronary arteries, unless compensated by improved collateral flow, must soon lead to cardiac failure.

Three distinct views exist as to the manner in which coronary flow is adapted to the work of the heart, viz., (1) that changes in aortic pressure play the dominant role, (2) that mechanical adaptive reactions between coronary resistance and arterial pressures are automatically brought into play, and (3) that chemical products of metabolism or nervous reflexes enhance coronary flow by dilating the coronary vessels.

The dominant role of aortic pressure in determining coronary flow has been established, but differences of opinion exist as to whether it increases with mean or diastolic pressures.[85] Since hypertension in-

volves an increase in the vigor of ventricular contraction and sometimes changes in heart rate as well, we cannot apply unreservedly conclusions reached under general conditions of coronary flow. This is particularly true since recent investigators hold contrary views regarding the effects of increased force of contractions, viz., (a) that they favor flow by massaging effects, or (b) reduce flow by greater compression of intramural vessels during systole.[85] Green, Gregg, and I[86] devised a method by which relative changes in systolic, diastolic, and cyclic flow could be compared in the same animal, although no absolute values for flow can be deduced. It consists essentially in recording simultaneously pressures in the central and peripheral ends of the ramus descendens anterior, subtracting the values of the latter from the former at consecutive points, and thus deriving a velocity curve. The areas under such curves express in arbitrary units the relative systolic and diastolic volume flows, and the sum of the two equals flow per beat. By studying changes in the same animal during hypertension, Gregg[87] found that the increase in flow is definitely greater than the rise of systolic pressure. Detailed analysis of curves showed that although systolic flow is somewhat increased, diastolic flow is especially augmented. The former occurs because the coronary resistance increases relatively less than aortic pressure during ejection, whereas the latter is chiefly due to elevation of pressure during diastole. The conclusion was thus reached that mechanical adaptations are quite adequate to insure the necessary improvement in coronary blood supply during hypertension. Nervous reflexes seem to act in just the opposite direction, for aortic and sinus caroticus reflexes induced by hypertension are said to diminish coronary flow.[88, 89] Since these reflexes were operative in some of Gregg's experiments, as indicated by slowing of the heart with increased tension, it can be said that the mechanical adaptation is much the more potent in adapting blood flow to cardiac work. Inasmuch as hypertension seems to increase coronary flow reflexly, it would seem, teleologically, that these reflexes serve their chief purpose in improving the blood supply of the heart under such conditions as shock, hemorrhage, dynamic failure of the ventricles, etc., in which the fall in pressures might otherwise cause serious impairment of coronary flow.

SUMMARY

1. Persistent experimental as well as human hypertension is probably due, fundamentally, to the operation of humoral agents, but nervous mechanisms may be temporarily or permanently active in addition.

2. The dynamic resemblances and differences between experimental and clinical forms of hypertension deserve further study by apparatus more suitable for recording pressures in animals, and the results require better integration with changes in heart rate.

3. The concepts of "central," "collective" and "effective peripheral" resistances are analyzed, and formulas for mathematical calculation of the latter are given.

4. Calculations of peripheral effective resistance by several formulas show that it is increased in various forms of human hypertension. But the magnitude of the increase does not necessarily correspond to the degree to which mean blood pressure is elevated, suggesting that other mechanisms are also concerned.

5. Old and new experiments are reviewed which demonstrate that an intensive narrowing of small vessels in the splanchnic area must occur in order to produce elevations of pressure equal to those found in hypertension. Evidence is lacking that constriction of limb vessels contributes essentially to the height of pressure in animals or in man.

6. Organic lesions are not generally distributed widely enough to account for the increased effective resistance, and there are good grounds for questioning whether significant narrowing occurs in restricted areas during life. The view that functional contraction of arterioles and prearterioles occurs is plausible, but we must not be too dogmatic in assigning the increased resistance entirely to arteriolar regions of the arterial tree. Some of the resistance may occur in vessels larger than prearterioles.

7. Diminished elasticity of the aorta and its immediate branches accentuates the elevation of systolic pressure and reduces the diastolic pressure. It accounts also for the large pulse pressure and the rapid diastolic decline of subclavian pulses in hypertension. The absence of a significant increase in diastolic pressure, far from denoting inconsequential involvement of peripheral vessels, is probably more often a sign of an extension of vascular changes to the larger vessels. It is questionable whether the division of cases of human hypertension into systolic and diastolic types serves any useful purpose.

8. Although sclerosis of larger vessels produces such changes, the suspicion has existed that aortic distensibility is also decreased, even when no pathologic changes are demonstrable. The view that in such subjects the aortic distensibility is decreased beyond that common for corresponding ages is supported by considerations arising out of new experiments on circulation models, on the perfused dog's aorta in situ, and by simultaneous records of aortic pressures and diameters in living dogs.

9. Studies of pulse velocity are not destined to supply practical proof of the involvement of larger vessels in man owing to the difficulty of measuring arterial distances with sufficient accuracy.

10. The hypothesis is suggested that the agent or agents that are concerned in the production of experimental and human hypertension tend to act along the entire arterial tree, causing contraction of the muscular elements. In the smallest peripheral vessels this narrows the lumen and

increases peripheral resistance; in the aorta and distributing branches it reduces capacity and extensibility.

11. Physiologically, the action of the left ventricle is not impaired as a result of the greater work imposed upon it by severe hypertension. In animals the output tends to increase, the mechanical efficiency is increased, and the economy with which the mechanical energy is utilized to propel blood is decidedly increased.

12. In order to do this the ventricle operates continually in the region of cardiac reserve, and if additional distention occurs, e.g., because of an added return of blood, as during exercise, it responds with decreased, rather than, as normally, with increased output. This explains the limited capacity for exercise and development of the "effort syndrome" on exertion.

13. Recent experiments in which changes in coronary arterial inflow under natural aortic pressures were studied by differential pressure curves indicate (1) that coronary blood flow increases as the systolic pressure, and (2) that mechanical adaptations between peripheral coronary resistance and aortic pressure, rather than nervous reflexes or chemical actions, are chiefly concerned.

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THE TREATMENT OF ANGINA PECTORIS BY METHODS WHICH APPEAR TO PROMOTE MORE ADEQUATE FILLING OF THE HEART*†

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IT IS generally agreed that anginal pain is related to myocardial ischemia or relative anoxemia.‡ The secondary metabolic changes in the myocardium presumably result in products which stimulate nerve endings, giving rise to symptoms grouped under the syndrome of angina pectoris. If these statements are true, we should expect that circumstances restricting the blood flow in the coronary circuit generally, or locally in relation to work done by the myocardium, would give rise to symptoms. In middle life or beyond, structural changes at the orifices or in the walls of the coronary vessels produce local barriers to the free passage of blood to certain parts of the myocardium. If these vessels retain their function of varying the caliber of the lumina, there will be circumstances when the flow may be increased or decreased in these areas, thus adding to or subtracting from the impediments of structural narrowing. The variability of function of the anastomosing branches from the remainder of the coronary vessels likewise influences the blood supply to the restricted areas.

If we list the functional disturbances predisposing to anginal pain, we shall find grouped under these headings most of the common clinical examples encountered in practice. The list by no means exhausts the possibilities suggested by this approach to the subject. Most of the forms of functional disturbances and the representative clinical types are obvious and have been mentioned by recent authors. The last group is, at the moment, hypothetic, but ultimately may be found to contain the great majority of patients presenting the anginal syndrome. It is this group with probable faulty filling of the heart and, secondarily, inadequate filling of the coronary vessels which is of particular interest.

For several years we[1] have observed and treated an increasing number of patients who presented a clinical syndrome of obesity and postural

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‡What is said concerning the myocardium may apply, likewise, to the base of the aorta, which is supplied by branches of the coronary arteries.

emphysema with variable circulatory symptoms, who, in addition, complained of symptoms related to disturbances in the spinal column, with radiculitis, who had symptoms associated with increased load and trauma on the weight-bearing joints, and who showed signs of hernias resulting from stresses on the abdominal wall. Many of these patients were referred to us originally because of the characteristic components of anginal pain.

Most of the patients were in the sixth or seventh decade of life, and a small group were in the fifth decade. In appearance, they were of the type generally spoken of as apoplectic, with florid complexion and moderate or marked corpulency. They complained of orthostatic dyspnea, i.e., they had dyspnea only in the upright position and could lie supine without discomfort. The spinal curves were all exaggerated, and there was marked lumbar lordosis, moderate or marked upper thoracic kyphosis, and an increased cervical lordosis. The exaggerated curves of the spinal column assisted the individual to "get under" the great weight of the protuberant abdomen. Under these circumstances, the lower ribs were shown to be in the inspiratory position, and the upper ribs in front were approximated and relatively fixed in the expiratory position. With the patient standing before the fluoroscope, the diaphragm was found to be one or two interspaces below the normal position; in ordinary breathing with the patient in the upright position the movements were limited, but when the patient was supine the diaphragm had a much greater excursion. It was assumed that the abdominal viscera together with the increased accumulation of fat served as a counterweight suspended from the diaphragm. When the patient was in the upright position, this weight interfered with the normal rise of the diaphragm during expiration, but when the patient was in the supine position it caused the diaphragm to rise higher in the chest during expiration and acted as an aid to respiration. The relaxation of the fascial sheet extending from the cervical fascia to the lumbar spine, and including the pericardium and central tendons of the diaphragm, also interfered with the normal movements of the diaphragm. It was apparent that the diaphragm, handicapped by the counterweight, the flared lower ribs, and the relaxed anchorages, was unable to maintain the tidal air at the normal level, and this probably explained the orthostatic dyspnea. Likewise, the resulting pulmonary emphysema seemed to be the cause of moderate polycythemia.

When studies were begun on this group several years ago it was obvious that some attempt should be made to improve the respiratory functions. Two therapeutic procedures were adopted: (1) A belt was devised[1, 2] which had two qualities: it was strong because it was designed to lift the counterweight, and elastic to permit expansion during inspiration and to assist in elevating the diaphragm during expiration. (2)

A reducing diet was prescribed to bring the patient's weight to a more normal level over a period of several weeks or months.

The results from the treatment of this group of patients have been very gratifying, as we have reported previously. During the past four years, I have been impressed with one result in a number of these patients that was wholly unexpected and, I think, unique. One after

TABLE I

FUNCTIONAL DISTURBANCES	AGENTS OR CLINICAL STATES
Effects of vasoconstricting drugs	Adrenalin Nicotine Ergotamine tartrate
Functional state causing vasoconstriction	Exposure to cold Alkalosis with tetany, associated with the anxiety states (hyperventilation) ? Effort syndrome Painful stimuli
Reduction of oxygen-carrying capacity of the blood	Severe anemia—relation of angina pectoris to primary or posthemorrhagic anemia; relief after restoration of the blood to normal levels Reduction of the level of red blood cells in polycythemia vera and in polycythemia associated with pulmonary emphysema Anoxemia caused by anesthetics Anoxemia in carbon monoxide poisoning
Fall in the level of systemic blood pressure	During sleep, in shock, in myocardial failure Aortic insufficiency with low diastolic pressure
Increased work of the heart	In hyperthyroidism, relieved by proper treatment During exercise, relieved by rest and vasodilator drugs Effects of thyroid extract in myxedema in older persons
Decreased filling of the heart and secondarily reduced filling of the coronary vessels	Paroxysmal tachycardia or shortening of diastolic phase from other types of tachycardia Postural hypotension Faulty movements of the diaphragm through counterweight of fat on viscera and after meals Organic obstruction of vessels returning blood to the heart

another of the patients who originally came complaining of anginal pain reported complete relief from this symptom. This relief began almost at once after the elastic belt was properly applied, and therefore was not caused by reduction in weight. The same result could perhaps have been obtained by reducing the counterweight in the abdomen through general reduction in body weight, but only after weeks or months of dietary restriction. These patients found that they had no further need for vasodilator drugs; and whereas formerly they could walk but short,

measured distances without pain, soon they could go long distances and even up inclines without any components of anginal pain whatsoever. To date I have seen approximately one hundred patients with typical symptoms of angina pectoris who have been treated in this manner, and the results have been uniformly excellent.

An exact explanation of the results described must await further study. It is believed that restored function of the diaphragm may be an important factor. In breathing, the movements of the diaphragm aid the return of blood to the heart through alternating changes in the intrapleural and intraabdominal pressures. With the patient in the upright posture, the relatively inactive diaphragm may materially impede the flow of blood from the abdominal viscera and the lower part of the body. It has been demonstrated in the patients with circulatory symptoms that in the upright position the blood and pulse pressures in the arms are very much lower than in the supine position. In some cases, no satisfactory auscultatory readings of arterial pressure could be obtained in the arms when the patients were in the upright position. There was very little difference in readings whether the arms were held horizontal or dependent. Studies on the circulation time and other studies have been started in order to find, if possible, the location of the alteration in function which relieves the pain.

SUMMARY

A brief report of observations on the relief of anginal pain, obtained by improving the movements of the diaphragm and presumably acting through more adequate filling of the heart and coronary vessels, is submitted. A positive means of prevention and treatment of anginal pain in the group of patients who are potential or actual sufferers from the syndrome is offered in the form of an elastic abdominal support supplemented by dietary restriction. It is probable that by these means the common catastrophe of coronary thrombosis may be postponed. While the great majority of persons who suffer from angina pectoris are obese, we have noted that a lighter type of elastic belt affords complete relief to the few individuals of slender build with the same syndrome. The elastic belt obviously can be of no value if the diaphragm is fixed through disease.

At the moment, the methods described would appear to be of distinct value to those who appear with well-established symptoms. However, if we are to prevent or postpone the development of the syndrome, we must apply this knowledge to the large group of sedentary workers, chiefly males, who are given to indulgence in good food beyond their needs. If our experience is duplicated by that of other clinicians, the way may be found to lessen the mounting toll of deaths in this group during middle life and beyond.

It is suggested that this approach to an understanding of problems concerned with the coronary circulation will have an application in the study of the arterial supply to other organs, especially to the brain, which in patients in this group is likely to be the seat of vascular accidents.

At a later date case histories and details of the studies that are now under way will be reported.

These remarks are dedicated by kind permission to Dr. James B. Herrick.

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VASCULARIZATION OF ATHEROSCLEROTIC LESIONS*

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RECENTLY much attention has been given to the vascularization of atherosclerotic lesions. Inferences have been drawn with reference to vascularization which do not appear to be justified from careful studies of the material.

THE CIRCULATION TO NORMAL ARTERIAL WALLS

The literature on this subject has been reviewed recently by Ramsey.[1] The general opinion of investigators is that vasa vasorum supply the adventitia and the outer third or outer half of the media of the human aorta. The nutrition of the intima is cared for by diffusion from the lumen. The inner portion of the media may be supplied by diffusion from two sources, the lumen and the vasa in the outer portion of the media. Much of the work reviewed by Ramsey was carried out in the last century. Subintimal vessels from the vasa were reported in the aorta of the cow and the whale,[2] in the human fetus, and in undernourished infants.[3] However, the evidence produced, even by believers in the theory that vasa vasorum supply the nutrition of the adult human intima, is feeble or lacking. Koester,[4, 8] who originated this theory, based it on the reasoning that all tissues should have a circulation. This overlooks the fact that the cornea and the adult lens, placed under conditions less favorable for nutrition than the arterial intima, are avascular. Efforts to demonstrate the presence of any vessels (blood or lymph) in the intima of normal human arteries have failed, save for rare questionable single vessels, even though the injection medium was a solution of nitrate of silver and not a suspension of pigment. The silver nitrate method failed also in the cornea.

Among recent papers on the subject of the circulation to arterial walls is that of Woodruff,[5] who injected India ink gelatin into the aortas of the horse and the dog and also injected vasa vasorum directly through specially devised glass cannulae. Vasa vasorum in the horse penetrated all layers of the media but terminated abruptly at the intimal junction. The general source of the vascular supply to the aortic walls in both the horse and the dog was from vasa vasorum arising from aortic branches. However, he found in 20 of 21 dogs that some vasa vasorum arose in the ascending arch directly from the aortic lumen and that these were distributed to the media. The number of vasa derived from the aortic lumen varied from one to seven. In the dog which showed no such vessels, the aorta was the seat of sclerosis. No circulation to the intima was disclosed in these studies.

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Robertson,[6] using for injection stable suspensions of pigment and radiopaque material, found discrete openings in the ascending aortas of two dogs. In two sections from human aortas minute nutrient vessels were seen penetrating the intima and branching in the inner third of the media. From studies of the aortas of the dog, the lamb, and man he concluded that the thoracic aorta is vascularized by a sheath of areolar connective tissue, richly supplied with vessels derived from the vessels of adjacent structures or from branches of the aortic efferent vessels, and forming an anastomosing network. The richest portions of this network were found about the arch and about the orifices of aortic branches. Vasa penetrated no further than the outer third of the media. Even the exceptional two minute vessels arising from the lumen of a human aorta were distributed to the inner third of the media. The intima, without exception, had no vascularization in normal aortas.

POSSIBLE RELATION OF THE LOCALIZATION OF ATHEROSCLEROTIC LESIONS TO THE DISTRIBUTION OF VASA VASORUM

Raynaud[7] in 1865 and Koester[8] in 1876, followed by many others, concluded that there was a relation between the vascular supply to the vessel wall and the localization of atherosclerotic lesions. Klotz in several studies supported this thesis. He demonstrated that syphilitic aortitis apparently owed its origin to infection extending along the lymphatics which accompany the vasa vasorum into the aortic wall.

The preferred localization of syphilitic aortitis, the ascending aortic arch, is in a region richly supplied with vasa vasorum. However, though the ascending arch is frequently the site of multiple, early, so-called pinhead atheromas, it is not a common site of advanced atherosclerotic lesions, except when these are engrafted on lesions of syphilitic aortitis. The early atherosclerotic lesions in this location tend to remain small and focal. The rich cholesterol deposits in these multiple pinhead lesions are removed by a mechanism which I have described[9]; the lesions subside and disappear, leaving a smooth intima without evident scarring. It should also be remembered that syphilis is an infection, whereas the lesions of atherosclerosis have at least no direct relation to infection.

Robertson concluded that a relation exists between the presence of certain lesions of the aortic wall and the distribution of the vasa vasorum. The richer the anastomosing network of vasa in a given locus, the greater the likelihood that lesions of the vessel would arise in that locus.

In a study of the very frequent localization of arteriosclerotic lesions about the orifices of the intercostal arteries, Klotz[10] argued that the mechanical theory of causation is wholly inadequate to account for this distribution of lesions, particularly when it is recognized that the intercostal orifices arise along the best supported portion of the aorta. Discussion of this question, however, should take into consideration that not only is the posterior wall of the aorta the best supported portion, but it is also for the same reason the portion of the wall which is relatively

fixed—anchored—by the intercostal vessels, while the rest of its circumference is comparatively free. The ascending arch of the aorta is the only portion of the vessel which is without branches and is unconfined. It is also the portion of the aorta, as indicated, which is least commonly the seat of advanced atherosclerotic lesions. The muscle waves of contraction and expansion of the aortic wall are unhampered in the free and branchless portion of the arch, but must meet with interruption about the orifices of vessels. Moreover, the interruption should be greatest about the orifices of those vessels which promptly enter fixed tissues, and permit little or no movement of the aortic wall, as is true of the intercostal arteries. That stresses due to interruption of the muscle waves are a factor in localization of atherosclerotic lesions is suggested by the frequent occurrence of lesions about the orifices of all of the aortic branches.

The atherosclerotic lesions about intercostal orifices are outstanding because once established they tend to be permanent. The common lesions of the ascending arch are as a rule temporary and disappear even at advanced ages, leaving little or no evidence of their presence. Lesions about intercostal orifices usually progress to the stage of permanent scarring and persist during the lifetime of the individual.

Klotz realized the futility of studies of advanced lesions in any effort to determine the etiology of arteriosclerosis and focused attention on the more informative early lesions. Atherosclerosis begins in the most superficial layers of the intima, in the region farthest removed from distribution of the vasa vasorum. It is difficult to understand how anything connected with the circulation through the vasa could influence the localization of such lesions. Klotz, from his study of early lesions, particularly in young persons who had died of infections, recognized this limitation and concluded that reactions in the intima, in many infectious diseases, may occur independently of, although simultaneously with, the inflammatory reactions about vasa vasorum. Animal experiments, in his hands, gave inconstant results.

MacCallum[11] concluded from his studies that: "It appears that there is but little evidence in favor of the idea that infections, whether acute or chronic, play a part in the pathogenesis of arteriosclerosis."

My studies of early lesions of atherosclerosis disclose that the process is not inflammatory in origin. Inflammatory cellular infiltration is absent in the earliest lesions and only rarely can a lymphoid or plasma cell be found in the early stages as the lesions enlarge and extend. When necrosis occurs, inflammatory cellular infiltration becomes common.

We may conclude, therefore, that materials of infectious origin which might be carried in the blood of the vasa vasorum play a minor part, if any, in the etiology of arteriosclerosis, or in the localization of lesions.

THE ORIGINS OF INTIMAL CIRCULATIONS IN ATHEROSCLEROTIC LESIONS

Just as the normal intima has no circulation, a careful study which I made of a large series of early atherosclerotic processes demonstrated

that these lesions also have no circulation. Only as the lesions enlarge beyond the early stages does a circulation appear. On the other hand, a study of over 200 advanced coronary lesions from 120 cases of coronary sclerosis disclosed that all advanced lesions are vascularized. It was intended to carry this study through a much larger series of coronary vessels, but the constancy of the findings (not a single exception) made this unnecessary. The laws of nutrition and growth govern this as they do all other reparative processes.

As we have seen, diffusion through the endotherial lining furnishes the nutritive support for the intima and in part at least the inner portion of the media. The nutrition of the early lesions of atherosclerosis is likewise cared for by diffusion. As the lesions enlarge, and particularly if fibrosis occurs, there comes a stage at which nutrition by diffusion is no longer adequate. Necrosis of the deep layers of the lesion, i.e., those farthest removed from the lumen, the source of nutrition, is practically constant. If the lesion is to enlarge beyond this stage, a new source of nutrition must be supplied and is provided through vascularization. The new vessels may originate from two possible sources. In the young particularly, new vessels may arise directly from the lumen, as I first reported.[12] Apparently, the distribution of these vessels may be limited in some cases to the diseased intima. Or, particularly in older persons, the new vessels may arise from vasa vasorum which penetrate through the inner layers of the media to reach the atherosclerotic nodules in the intima. The formation of these new vessels to the intima from either source is a late phenomenon, occurring only after the lesions as they enlarge have exhausted the possibilities of nutrition by diffusion.

Winternitz, Thomas, and Le Compte have revived the question of possible vascularization of the normal intima in a paper entitled "Studies in the Pathology of Vascular Disease."[13] They indicate that they are presenting new knowledge which will aid in the understanding of the anatomical processes involved in atherosclerosis. They deprecate the value of contributions concerning the pathology of the various processes, which have proved disappointing.

"Present day descriptions of the process differ in no essential from those of Morgagni save that they are more brief and employ a somewhat changed nomenclature. The histological picture and its interpretation is not different from that of the time of Virchow." It is evident that the authors of this paper are lovers of the older medical literature. There is only one reference to a modern study on atherosclerosis in their short bibliography. Morgagni died in 1771. Virchow died in 1902. Aschoff and the modern German school, Anitschkow and the Russian school, Klotz and MacCallum and the American school have added at least some data in the decades which have elapsed since Virchow's death.

The embryological work of Bremer[14] is referred to as establishing the developmental basis for a vascular pattern such as is found in the aorta of the cow. In this animal small vessels arise from the lips of the

branches, and coursing *under* the intima anastomose with minute vessels arising from the lumen. Winternitz and his associates agree that this pattern is difficult to show in all human arteries. "Frequently, however, in the coronaries and in the abdominal aorta very minute vessels are encountered arising independently from the wall and running to the adventitia where they anastomose in the rich adventitial plexus. Occasionally such vessels, as they penetrate the aorta, are seen to give off small branches to the intima and media. After examination of many human arteries it must be emphasized that vessels are seldom demonstrable in the intima or in the inner half of the media when no irritative, obliterative or morbid process is present." The last sentence indicates that the lesions on which this paper was founded were advanced lesions. Atherosclerosis and its effects are the commonest and most important agencies responsible for irritative, obliterative or morbid processes in the arterial intima, excluding syphilis and the repair at the site of the ductus arteriosus orifice. How the study of advanced lesions can be very helpful in determining the etiology of atherosclerosis is difficult to comprehend.

The authors of this paper endeavor to emphasize the importance of hemorrhages through rupture of the delicate vessels found in the lesions. One gets the impression that hemorrhages are early phenomena and etiologically important in atherosclerosis. An interesting demonstration of the translucency of the normal aortic intima can be made by injecting minute drops of oxalated blood into the intima or the subintimal media. If the hypodermic needle is thrust diagonally through the back of the aorta the blood may be placed with some exactness. The specks or colored hillocks of the injected blood could not be overlooked even by a tyro in pathology. Atherosclerosis is perhaps the commonest chronic human disease; the aorta is a favorite site for localization of its lesions, and yet such hemorrhages into the normal aortic intima have not been reported. A marked increase in the thickness and opacity of the intima could be the only means of cloaking such a hemorrhage from view, and this type of change could be produced only in advanced lesions.

An effort is made to account for the cholesterol found in atherosclerotic lesions as arising from the blood of these hemorrhages. "It is reasonable to suppose, therefore [i.e., because of the accumulation of fatty material at the site of a hemorrhage], that this fatty material is derived from, and eventually replaces, the blood of the original hemorrhage," etc. Normal blood contains not more than 820 mg. of total fats per 100 c.c. of blood, less than 1 part in 100. But it is agreed that most of the fat in atherosclerotic lesions is cholesterol. Normal blood contains not more than 230 mg. of cholesterol in 100 c.c., less than 1 part in 400. It is hardly reasonable to suppose that fatty material present in blood in these minute amounts could replace the blood of the original hemorrhage or account for the massive collections of cholesterol found in atherosclerotic lesions. It is generally agreed that the cholesterol in

these lesions is transported to the site of the lesions either in macrophages or free in the blood stream, and does not arise locally from hemorrhages.

Notwithstanding the claims of Winternitz and his co-workers, it must be concluded that:

1. The normal intima is not vascularized, and that intimal vessels are found only in connection with vascular lesions in which repair has taken place.

2. Since the vessels arise as the result of repair processes, i.e., since the lesions are advanced atherosclerotic lesions, the hemorrhages from such vessels must be late phenomena and are, therefore, not of etiologic importance.

3. Cholesterol found in atherosclerotic lesions is transported to the site in macrophages or as free or ester cholesterol in the blood, and does not arise locally except perhaps in small amounts.

4. The laws of nutrition and growth still hold in atherosclerotic lesions.

Finally, to quote Klotz on the etiology of atherosclerosis: "It may be well to indicate that the mode of origin or the previous course of a fully developed plaque of endarteritis cannot be determined by a study of the old lesions alone, and it is futile to hold controversy over such an undeterminable problem. A study of the earliest stages of the lesions in the tissues of man is still the most secure upon which to base conclusions."

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THE USE OF METRAZOL IN COMPLETE HEART BLOCK WITH ADAMS-STOKES SYNDROME

Report of Four Cases

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COMPLETE heart block is infrequently encountered in medical practice; yet its presence always attracts considerable attention, especially when it is associated with the Adams-Stokes syndrome.

At present there is no entirely satisfactory treatment of heart block and Adams-Stokes syndrome. A number of drugs have been suggested from time to time, each with its initial series of good results and, later, almost invariably with its disappointments. Atropine sulfate in doses of 0.3 to 1.2 mg. (1/200 to 1/50 grain) is most commonly used. Its untoward side effects, viz., dryness of the mouth, dilatation of the pupil and gastrointestinal distress, restrict its continuous use. More important is the number of cases in which it does not increase ventricular rate nor decrease the periods of syncope. Barium chloride has been successfully used by many.[1] However, toxic manifestations, such as extreme breathlessness, irregular acceleration of the ventricles, and signs of collapse, have followed the use of 60 mg. (1 grain) doses.[2] In periods of ventricular asystole epinephrine has been employed frequently.[3] Levine and Matton[4] used it effectively by direct injection into the heart of a patient who had ventricular standstill lasting five minutes. Small daily doses of epinephrine have often been helpful in reducing the number of Adams-Stokes attacks. The necessity of repeated hypodermic injections and the pronounced sympathetic effects are hindrances to the prolonged use of this drug. Ephedrine is often effective in terminating the syncopal attacks and increasing the ventricular rate,[5] but continued oral administration also causes wakefulness, flatulence, and anorexia, often prohibiting the further use of the drug.

In view of the many causes of heart block and Adams-Stokes syndrome, their not infrequent tendency to cease spontaneously, and the different medication suggested in the past, it is with some scruples that another drug is recommended, yet the writer's observation of the effect of metrazol prompts him to say that in some cases it is beneficial, and that it compares favorably with any of the other drugs now in use; it has the further advantage that in cases in which it is effective it may be used with no apparent untoward side effects for prolonged periods.

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Metrazol was given to four patients with complete heart block and Adams-Stokes seizures. Two of them were greatly benefited by the drug; in the other two it was of no value. Case 3 was that of a patient on the medical service of Dr. Don C. Sutton, and I am indebted to him for permission to study it.

REPORT OF CASES

CASE 1.—M. L., a white woman, aged 78 years, was first seen on April 19, 1933, during a typical Adams-Stokes seizure. She had her first syncopal attack in 1925, at which time a physician made a diagnosis of complete heart block. After several days of rest in bed she resumed her former activities and was without symptoms for two and a half years, when a second attack occurred. Much like the first seizure, it lasted a few hours; it was followed, after a year and a half of well-being, by a third attack. During the next year the symptoms progressed rapidly, and the first break in cardiac compensation occurred. Prolonged rest in the hospital reestablished compensation and provided electrocardiographic evidence of A-V block with a ventricular rate of 40-44 beats per minute. Her symptoms progressed slowly, and she was given camphor in oil, barium chloride, epinephrine, and, finally, atropine. The latter was the only effective drug; it reduced the number of attacks from 50 to 4 per week. On Feb. 8, 1933, a second failure of compensation with considerable peripheral edema was observed. Atropine sulfate was discontinued. Five weeks later compensation was partially regained, but the syncopal seizures were more numerous than before. Neither the oral administration of atropine sulfate in doses of 0.64 mg. (1/100 grain) every four hours nor subcutaneous injections of 0.8 mg. (1/75 grain) every three hours gave any relief, and toxic symptoms and unpleasant side reactions forced us to discontinue this drug. Epinephrine, ephedrine, barium chloride, digitalis, camphor in oil, and pituitary extract were similarly ineffective.

Physical Examination.—The respirations were deep, labored, and slow (5 per minute). There was moderate atherosclerosis of the peripheral vessels. The pulse was regular and full, and its rate was 36 per minute. The blood pressure was 178/138. The apex beat was diffuse and was located in the fifth left intercostal space at the anterior axillary line. The heart was enlarged both to the right and left; the borders were 5 and 13 cm., respectively, from the midsternal line. No murmurs were audible, and the heart tones were loud and distinct. A few moist râles were heard over the pulmonary bases posteriorly, the edge of the liver was 5 cm. below the costal margin, and a moderate amount of edema of the legs was present.

Subsequent Course.—Several subcutaneous injections of epinephrine (0.5 c.c. of a 1:1000 solution) were given without any apparent benefit. One cubic centimeter of metrazol was given subcutaneously, and her respiratory rate increased markedly within five minutes. The injections of metrazol were repeated every five minutes, and within thirty-five minutes she regained consciousness; her respiratory rate was 20 and her pulse rate 62 per minute. One tablet of metrazol was given every half hour for the next seven hours. At the end of this period she had continued to improve so much that it was decided to allow her to rest and sleep. She awoke refreshed, but her pulse rate had fallen to 48 per minute. One tablet of metrazol every hour when she was awake was given during the rest of the week. No syncopal attacks were seen, her pulse ranged from 50 to 74 per minute, and her compensation improved. This striking effect aroused our curiosity so much that atropine sulfate, in doses of 0.3 mg. (1/200 grain) every second hour, was substituted for the metrazol. Six hours after this change in medication the first

Adams-Stokes syndrome appeared. During the next four days the attacks increased in number and severity. Again the medication was reversed; metrazol was given, and atropine discontinued, but it was several days before she was free from syncope. Improvement continued, the pulse rate remained above 54 per minute, and she was free from attacks during the next week. She felt better and despite advice to the contrary she got up and did some housework. There were several mild attacks, and she went back to bed. After that she failed rapidly and died two days later.

CASE 2.—E. D. L., an 83-year-old widow, had been a resident of the Presbyterian Home of Evanston for more than twelve years, during which time she had had a systolic blood pressure of 200 mm. Hg. She was first seen on July 30, 1936, after she had fallen twice while attempting to dress herself.

Physical Examination.—The patient was a moderately obese woman with a considerable degree of atherosclerosis of the peripheral vessels. The heart was moderately enlarged to the left and the apex beat was localized just beyond the midclavicular line. The blood pressure was 220/94, and the pulse rate was 58. Otherwise the findings were normal. She was advised to rest more, put on a salt-poor diet, and given theobromine sodium salicylate in doses of 0.6 gm. (10 grains) t. i. d.

Subsequent Course.—A week later the heart rate fell to 48 per minute, and there were many vertiginous attacks. An electrocardiographic tracing showed complete heart block. She was given one tablet of metrazol thrice daily after meals. Within a few days the attacks disappeared, but there was considerable unsteadiness of her gait. The dosage of metrazol was doubled in an effort to relieve the ataxia, which was thought to be caused by atherosclerotic changes in the arteries of the spinal cord. After four weeks of this new regime she felt better than she had in the previous two years; she was free from attacks, could walk better, and her pulse rate was 62 per minute. Metrazol was discontinued for several days, whereupon the Adams-Stokes syndrome reappeared, and the heart rate fell to 44 per minute. After a two-week period during which she took metrazol tablets every four hours she regained her previous good status and the pulse rate rose to 60 per minute. Again, the metrazol was discontinued and atropine sulfate in doses of 0.3 mg. (1/200 grain) was given thrice, then four times, daily. During the second week 0.6 mg. (1/100 grain) was given q. i. d., but there were still occasional periods of syncope and the pulse rate was 48. The extreme dryness of her mouth forced us to abandon the use of atropine and return to metrazol, which has kept her comparatively free from the Adams-Stokes attacks for the past eighteen months.

CASE 3.—C. W., a 58-year-old Pole, entered the Cook County Hospital Feb. 18, 1935, complaining of attacks of dizziness and fainting. He had been in good health until 8 years before admission, when he had had a severe respiratory infection of undetermined nature. This left him somewhat weak, and there was some dyspnea on exertion. Later there were occasional periods of dizziness that lasted 20 to 40 seconds. They grew progressively worse, so that two weeks prior to entrance he was forced to give up his work as a machinist. He denied any venereal infection and used alcohol moderately.

Physical Examination.—The patient was a slender, somewhat anemic man who appeared to be healthy. The apex beat was just outside the nipple line, and a loud systolic murmur could be heard over the aortic area. The blood pressure was 168/82. There was moderate atherosclerosis of the peripheral vessels; the pulse rate was 36.

An electrocardiogram showed complete block with normal ventricular complexes and a ventricular rate of 40 per minute.

He was given one tablet of metrazol q. i. d. for four days, without any effect on his pulse rate. The dose was doubled for the next three days and trebled the next week. Then he was given 1 c.c. of metrazol subcutaneously every two hours for the next week. His ventricular rate varied from 32 to 40 during that time, and he did not improve. Atropine sulfate in doses of 0.3 mg. (1/200 grain) was given subcutaneously for the next week, and within one day's time he felt better and his ventricular rate rose to 64. After a week of this treatment his Adams-Stokes seizures disappeared. The following week he was given no medication, and the ventricular rate fell to 40 per minute. Large doses of metrazol, 4 tablets every two hours and 2 c.c. every two hours subcutaneously, were ineffective. He was then given atropine sulfate in doses of 0.6 mg. (1/100 grain) after meals, which afforded him such complete relief of his symptoms that he left the hospital with a ventricular rate of 66.

CASE 4.—W. H. S., a white man 76 years old, was admitted to the medical service of the Research and Educational Hospital July 2, 1938. For three years he had suffered transient attacks of syncope which had become progressively worse during the preceding four months; they occurred from three to ten times a day, lasted from several seconds to a few minutes, and sometimes were so severe that he fell.

Physical Examination.—The skin and mucous membranes were pale, and there was a coarse tremor of the tongue. There was moderate emphysema of the lungs which made it difficult to percuss the cardiac borders. A soft systolic murmur was heard over the aortic area, and the heart tones were distant. The heart rate was 24 per minute, and the blood pressure was 154/42. Marked atherosclerosis of the peripheral arteries was noted. There was diffuse enlargement of the prostate.

Laboratory Examination.—The erythrocytes numbered 4,100,000 per cubic millimeter; the hemoglobin was 12.2 gm. per 100 c.c.; the Kahn reaction on the blood was negative. Except for a nonprotein nitrogen of 59 mg. per 100 c.c., the blood was chemically normal.

Subsequent Course.—During the first twenty-four hours in the hospital the patient had three attacks of syncope approximately one minute in duration. These attacks were not preceded by an aura; no period of stupor followed them; the patient did not bite his tongue. An electrocardiogram taken July 5 showed an auricular rate of 50 and a ventricular rate of 22 per minute. At times there was marked auricular slowing and standstill. Metrazol was given in doses of 1 c.c. subcutaneously every three hours. A series of electrocardiographic tracings was taken before and after a single metrazol injection. They showed some increase in auricular rate. After several days of metrazol treatment both by mouth and subcutaneously, his condition was much worse with increased periods of stupor, so that the drug was discontinued. Epinephrine (1:1000) was given subcutaneously in 0.3 c.c. doses every three hours with almost immediate benefit. The next day 2 c.c. of metrazol were injected intravenously while a continuous electrocardiogram was being taken. A comparison of this record with a control tracing taken before the injection, as well as with those taken at five-minute intervals afterward, failed to show any changes. Later, epinephrine was again discontinued and atropine and ephedrine in full therapeutic doses were tried. His pulse rate fell to 20-28 per minute, and he again became stuporous, so that epinephrine had to be given. The latter improved his condition sufficiently to allow him to be transferred to a convalescent home two weeks later.

COMMENTS

Metrazol, or pentamethylenetetrazol, was first introduced by Hildebrandt,[6] who found that it had certain advantages over camphor. It is water-soluble, can be sterilized easily, and acts promptly after subcutaneous injection mainly by stimulation of the vasomotor and respiratory centers. Cardiazol, as metrazol is called in Europe, frequently has been reported as a successful remedy for circulatory collapse.[8] The careful animal experiments of Camp[7] failed to demonstrate any direct action on the heart, nor did a single intravenous injection of metrazol in a patient (Case 4) show any electrocardiographic changes. There are but few similar references in the American literature.[9] Recently it has been given in large doses (5-7 c.c. of a 10 per cent solution) intravenously in the treatment of schizophrenia over extended periods without any apparent ill effects, so that prolonged administration evidently is not harmful.[10] A probable explanation of the beneficial effect of metrazol in complete heart block with the Adams-Stokes syndrome is that it stimulates the vasomotor tone and respiration. No explanation is offered for the ineffectiveness of metrazol in the other two patients, except that similar observations have been noted wherein one drug was ineffective and others were effective. This emphasizes the statement that there is at present no single, entirely satisfactory treatment of heart block.

CONCLUSION

Metrazol was given to four patients with complete heart block and the Adams-Stokes syndrome. Two of them were greatly benefited by the drug and two were not. Apparently the action of metrazol is on the vasomotor and respiratory centers, not on the heart.

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THE USE OF QUINIDINE IN THE TREATMENT OF ARRHYTHMIAS AND TACHYCARDIAS CAUSED BY DIGITALIS INTOXICATION

With a Note on the Possibility of "Spontaneous Redigitalization" Following Rapid Diuresis*

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DIGITALIS, under certain conditions, may defeat its own purpose. It may accelerate cardiac failure and do so in a manner so insidious that the undesirable effect may be entirely overlooked. Such poisoning is probably on the increase. The demonstration of the usefulness of large doses has led to a feeling of overconfidence and indifference to the double-edged quality of this great remedy. The studies of Drew Luten,[1] and of Bellet and McMillan[2] at the Philadelphia General Hospital, leave no doubt that the classic clinical signs of intoxication are not constantly exhibited, and that the electrocardiographic changes may be the first evidence of poisoning and the most reliable guide to the use of the drug.

This is a report of two pertinent cases in which serious digitalis poisoning manifested itself by cardiac arrhythmias, namely, nodal and ventricular tachycardia and auriculoventricular dissociation. These disturbances continued despite withdrawal of the drug. Quinidine therapy was useful in restoring normal rhythm in one patient, but was of no avail in the other.

REPORT OF CASES

Case 1.—G. A., a 65-year-old white man, had been treated for hypertensive cardiovascular disease at the heart clinic of Mt. Sinai Hospital for four months, during the larger part of which time he received 3 grains of digitalis per day; it was not continuously administered, and at no time was there evidence of digitalis intoxication. Despite treatment his cardiac decompensation progressed, and he was admitted to the service of Dr. A. Trasoff, March 9, 1937, with edema of the legs, left-sided hydrothorax, and enlargement of the liver. An electrocardiogram made the next day showed normal sinus rhythm, left axis deviation, and inversion of T_1; the tracing was similar to those which had been taken previously. Four and one-half grains of digitalis and 15 grains of theophyllin per day were prescribed. Two c.c. of mercupurin were administered intravenously, and this dose was repeated within three days. Diuresis was rapid, and on March 15, six days after admission, the peripheral edema had practically disappeared. On that day, however, the pulse

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rate, which had declined to 66, suddenly became rapid, at first 140 and then 180 per minute. An electrocardiogram revealed auriculoventricular dissociation (Fig. 1*A*). This series of events, namely, ventricular tachycardia following sinus bradycardia, was considered indicative of digitalis intoxication, especially in the absence of other untoward developments such as coronary occlusion. The drug was stopped, and 4 grains of aminophyllin were given intravenously, but on the next day, March 16, the arrhythmia persisted at increased rates, the auricular 150, the ventricular 220, per minute. The patient became apathetic and confused but did not vomit or show other evidence of gastrointestinal disturbance. On March 18 an electrocardiogram showed what apparently was auriculoventricular rhythm with a rate of 230 per minute (Fig. 1*B*). A P-wave immediately followed the QRS complex in both the direct and indirect leads. At such rapid rates accurate diagnosis becomes diffi-

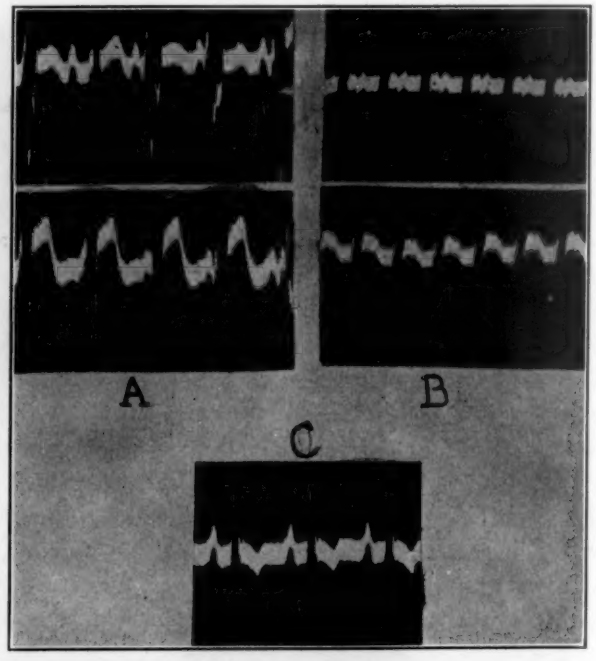

Fig. 1.—Case 1. *A*, Leads II and IV (Wolferth), March 15, 1937, auriculoventricular dissociation, auricular contractions (P), rate 157, ventricular, 162 per minute. *B*, Leads II and III, March 18, 1937, nodal (?) paroxysmal tachycardia, rate 230 per minute. The P-wave follows QRS regularly. *C*, Lead II, March 21, 1937, restoration of normal sinus rhythm following the use of quinidine.

cult, and since so rapid a nodal rhythm has not previously been recorded, the diagnosis of nodal paroxysmal tachycardia must remain tentative. Digitalis had not been taken for three days, but the cardiac arrhythmia constantly assumed a more serious aspect, and the patient's condition became critical. Morphine and aminophyllin were of no help. Twenty grains of quinidine sulfate, divided into four equal doses, were given by mouth in the next twenty-four hours (March 18), with the result that there was a remarkable slowing of the heart rate. This was followed by marked variation in the rate, between 85 and 160 per minute, the more rapid rate appearing in the night and early morning hours. Apparently no midnight dose had been administered. Quinidine was stopped on March 19, and on the following day the arrhythmia returned, the heart rate being 190 to 200 per minute. Twelve grains

of quinidine divided into three equal doses were given by mouth at three-hour intervals, with a consequent resumption of normal sinus rhythm corroborated by an electrocardiogram. The medication was continued for three days because of the appearance of short runs of auricular extrasystoles and nodal rhythm in daily electrocardiographic tracings. After this period normal sinus rhythm was constant.

CASE 2.—H. B., a 58-year-old white man, was admitted Sept. 30, 1937, to the Mt. Sinai Hospital in a state of cardiac decompensation. He had had edema of the legs for the preceding ten months. We were not aware at the time that he had taken 3 grains of digitalis and 3 grains of squills (in Niemeyer pills) per day for many weeks. The patient was drowsy, orthopneic, cyanotic, and markedly edematous. Cardiac enlargement, pulmonary congestion, and enlargement of the liver were noted. An electrocardiogram made on October 1 showed auricular fibrillation; the ventricular response was almost regular at a rate of 96 per minute, and there were occasional ventricular extrasystoles. The S-T deviations in Leads I, II, and IV sug

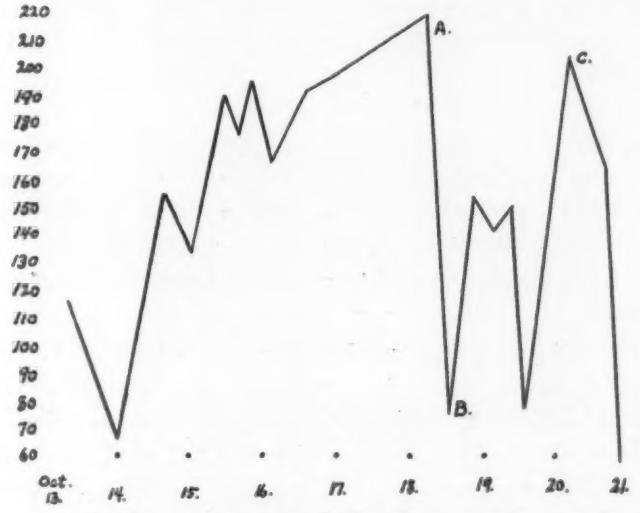

Fig. 2.—Case 1. The effect of quinidine on digitalis tachycardia; *A*, quinidine first used; *B*, quinidine therapy stopped; *C*, its resumption.

gested the effect of previous digitalis therapy. The patient received 6 grains of digitalis, 4 grains by mouth, and 1 ampoule of mercupurin intravenously in the next forty-eight hours. There was a urinary output of 90 oz. on the following day. The amount of digitalis prescribed was moderate, but on October 3 the administration of the drug was stopped because the patient vomited many times and the pulse rate was 60 per minute. On October 7 an electrocardiogram revealed normal sinus rhythm, but the S-T deviations were again suggestive of a digitalis effect. The unsatisfactory clinical progress led again to the intravenous use of mercupurin in 2 c.c. doses on October 6 and 8. An electrocardiogram made on October 9, six days after the last dose of digitalis, showed unmistakable evidence of digitalis poisoning. In the same tracing there were (1) A-V dissociation, and (2) long runs of coupled ventricular extrasystoles. On October 10 the dissociated rhythm continued; the auricular rate was 150 per minute; the ventricular, 136. The patient remained drowsy but did not vomit at this time. The apparently delayed and cumulative effect of digitalis was puzzling. One c.c. of mercupurin on October 12, and 2 c.c.

on October 14, were administered intravenously, but the arrhythmia persisted and the patient became semistuporous. On October 14 an electrocardiogram showed that in addition to the continued A-V dissociation the QRS complex had become sufficiently altered in shape to indicate that its origin was either low in the A-V node or possibly in a branch bundle (Fig. 4*A*). The patient refused oral medication, and inasmuch as preparations of quinidine for intravenous use were not available, we employed quinine sulfate intramuscularly in 2½ grain doses every three hours, but the patient died (Oct. 16) before this treatment could have had much effect. The clinical diagnosis was arteriosclerotic cardiovascular disease, cardiac decompensation, and digitalis poisoning. Permit for necropsy was not obtained.

DISCUSSION

The arrhythmias caused by digitalis may be placed in two groups: the first featured by disturbances in conduction, the second by evidence of increased irritability of the heart muscle. They may appear in combination in any patient. The first group does not cause serious concern, since even marked bradycardia and heart block will disappear soon after withdrawal of the drug. The second group is characterized by extrasystoles, at first isolated, later in coupled rhythm, and finally in ectopic tachycardias. Ventricular tachycardia is not uncommon and unfortunately its recognition in many cases is possible only by electrocardiographic examination. Many instances of this type of digitalis poisoning are serious; some of them are undoubtedly instances of fatal intoxication. Our patients were in this group.

Since quinidine has been used in the prophylaxis and treatment of the ventricular tachycardias,[3, 4] we thought that it might be useful in these cases of digitalis poisoning. However, there are certain well known contraindications to the use of quinidine, particularly the presence of marked cardiac enlargement and congestive failure.[5] Possibly the majority of patients who take digitalis continuously have one or both, and the advent of uncontrolled digitalis tachycardia in such cases places physicians in a serious dilemma. Ordinarily most of them would hesitate to employ quinidine, whose beneficial action is based on a toxic effect, in a patient who is already the victim of poisoning by another drug. It becomes a matter of the choice of the lesser evil. Certainly if tachycardia and arrhythmia continue in a diseased heart over a prolonged period of time, death is to be expected. Any attempt to restore normal heart rhythm would appear to be justified. Quinidine accomplished this in a striking way in our first case. The temporary benefit of insufficient treatment was demonstrated in this patient. The resumption of normal rhythm was followed within six hours by return to the previous arrhythmia; the repeated and finally permanently successful effect of quinidine made it clear, however, that the initial success was not merely a matter of coincidence (see Fig. 2).

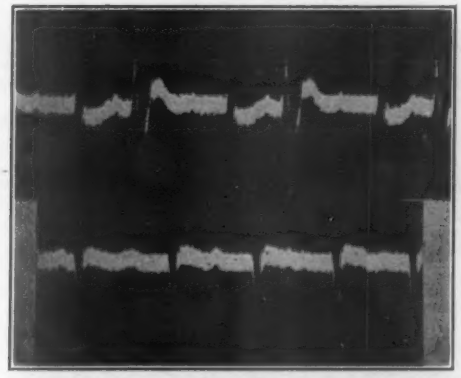

Fig. 3.—Case 2. Leads I and III, Oct. 9, 1937, auriculoventricular dissociation. In Lead I there is coupling of ventricular extrasystoles (bigeminy). This was thought to be partial heart block (prolonged P-R interval) with coupled extrasystoles; with cessation of bigeminal rhythm, the A-V dissociation was obvious. The auricular rhythm is slightly irregular, the rate 130; the ventricular rate more irregular (Lead III), 115 to 125 per minute. The administration of digitalis ceased six days before this tracing, but in the interval mercupurin was used intravenously repeatedly.

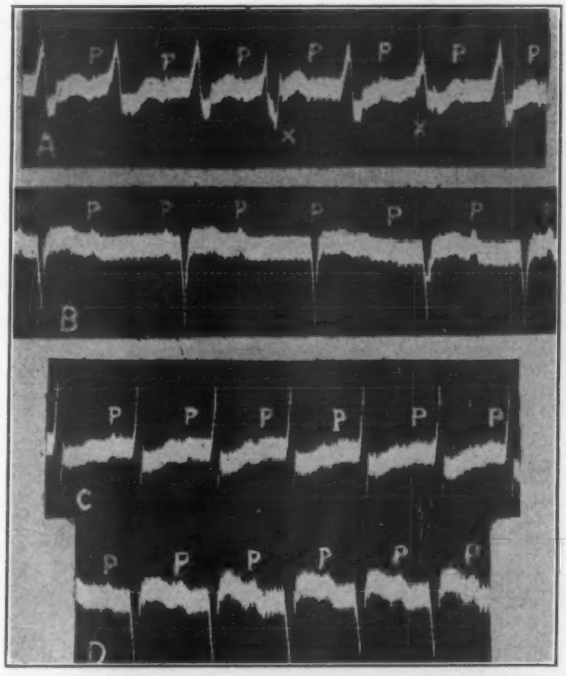

Fig. 4.—Case 2. *A*, Lead I, Oct. 14, 1937, paroxysmal ventricular (?) tachycardia, rate 125 to 130, following continued use of mercupurin. The shape of the ventricular complexes is altered, and some of them suggest multifocal origin (X). The independent auricular waves (P) are barely seen; rate 136 per minute. *B*, Another tracing, Lead III, same day; continued A-V dissociation, the auricular rate 130, the ventricular, somewhat irregular; 78 to 68 per minute. *C* and *D*, Leads I and III, Oct. 15, 1937 (one day before death). Continued A-V dissociation, the auricular rate 142-150, the ventricular 146-157 per minute.

Quinidine was inadequate in the second case; its intravenous use might have altered the situation.[6] There are other features in the case that are worthy of comment. The amount of digitalis administered in the hospital was small, yet poisoning quickly developed and, contrary to clinical experience, became progressively severe despite withdrawal of the drug. The long continued use of the drug prior to hospitalization had not been known. In the light of this history the influence of diuretic medication on bringing digitalis back into the circulation from collections of edema fluid[7] appeared to be of some importance. The intravenous injection of mercupurin was frequently repeated when it was realized that digitalis could no longer be employed. We now believe that there was a distinct relationship between the forced diuresis and the appearance of cumulative digitalis poisoning. A fairly large hydrothorax was undoubtedly present, but thoracentesis two days before death had yielded only 100 c.c. when the patient complained of pain, which necessitated withdrawal of the needle. This small amount of fluid gave rise to a typical digitalis reaction in a frog heart (Straub preparation). There was at first a sustained increase in ventricular function, followed by its gradual diminution and finally by arrest of the ventricular systole. The pleural fluid also gave a strongly positive reaction in the Keller-Kiliani test.[8, 9] A control pleural nondigitalized fluid from another patient with cardiac failure gave a negative frog reaction. These tests are only qualitative, and the positive reactions that may be obtained in body fluids during or after digitalis therapy do not by any means indicate that marked intoxication has developed. Nevertheless, the reactions in this case were so definite and the amount of pleural fluid tested was so small, that one may safely assume that a considerable concentration of digitalis, or of "digitalis bodies," was present in the fluid. Review of the clinical course of the first patient strongly suggests a similar effect of rapid diuresis. There again digitalis poisoning became increasingly severe despite withdrawal of the drug. The significance of two such experiences can be easily overestimated; they lend support, however, in our opinion, to the belief that spontaneous redigitalization is possible in a patient who, despite long continued digitalis therapy, develops dropsy and is then subjected to rapid diuresis.*

SUMMARY

Quinidine therapy was strikingly successful in one patient in arresting a serious cardiac arrhythmia due to digitalis poisoning. Its failure in a second case may be ascribed in part to inadequate dosage, and in

*Since completion of this report we have seen five more patients in whom the clinical course showed a mobilizing effect of diuretics on digitalis. One patient had fatal digitalis poisoning; both the chemical and biologic tests for digitalis were strongly positive with pleural fluid.

part to the state of advanced cardiac decompensation. Another factor, however, was a cumulative effect of digitalis, possibly caused by a mobilization of that drug in the circulation during diuresis.

We wish to thank Dr. A. Trasoff, Chief of Medical Service B, Mt. Sinai Hospital, for permission to study these cases, and Dr. Carl Schmidt, Department of Pharmacology, Medical School of the University of Pennsylvania, and Dr. J. Reinhold, biochemist of the Philadelphia General Hospital, for their help in performing the biologic and chemical tests for digitalis in the pleural fluids.

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ACUTE NEPHRITIS WITH CARDIAC FAILURE

Report of Two Cases*

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A RECENT report by Master, Jaffe and Dack[1] re-emphasizes an old but little known observation, namely, that acute glomerulonephritis is sometimes accompanied by cardiac failure. This failure is predominantly left ventricular, and may occur early in the course of the disease, even before there is evidence of renal damage. In their study of twenty-four cases of acute nephritis they found that the electrocardiogram was significantly abnormal at some stage of the disease in nineteen (these abnormalities consisted of changes of the T-wave in Leads I, II, and IV, absence of the initial positive deflection in the precordial lead, and prolongation of the auriculoventricular conduction time); that the systolic and diastolic pressures were invariably high; that left ventricular failure was present in eight cases; and that in no instance was there unequivocal evidence of right ventricular failure. They regard acute glomerulonephritis as a systemic vascular disease which may involve the heart as well as the kidneys, and referred to Stone's report[2] of a case of arteriolitis of the heart in acute nephritis, but neither in one case from their own series nor in six others were they able to demonstrate gross anatomic or significant microscopic abnormalities of the heart.

We wish to report the following two cases because they appeared to be examples of acute nephritis accompanied by cardiac failure. The fact that extensive histologic changes were found in the arterioles opens up a wide field for speculation as to the nature of the underlying pathologic condition.

REPORT OF CASES

Case 1.—The patient was a white man, 27 years of age, who was admitted to the University Hospital Oct. 2, 1935, complaining of shortness of breath and edema. Five weeks prior to admission he developed pharyngitis, lymphadenitis, and a generalized erythematous rash that lasted three or four days and was followed by desquamation. His shortness of breath began with the onset of desquamation and grew progressively worse until it reached the stage of orthopnea. One week prior to admission he developed edema of the lower extremities. No edema of the face was noted. There was no gross hematuria.

At the time of admission the clinical appearances were those of severe congestive heart failure. The patient had orthopnea, pleural effusion, ascites, and edema of the

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lower extremities. The heart sounds were faint, and gallop rhythm was present. The blood pressure was 210/120. The liver extended about an inch and a half below the costal margin. Ophthalmoscopic examination revealed one small hemorrhage in each fundus.

The urine contained albumin (graded ++) and blood (graded +++, Meyer's test), together with a few casts. The erythrocyte count was normal. The blood urea nitrogen was 11.9 mg. per cent, the creatinine 1.0 mg. per cent, and the uric acid 5.2 mg. per cent. The total plasma protein was 5.77 per cent (albumin 2.71, globulin 2.55, fibrinogen 0.51). The urea clearance was 75 per cent of normal. The plasma cholesterol was 250 mg. per cent. The blood Wassermann and Kahn reactions were negative.

The patient was kept at rest in bed and given a salt-free diet of normal protein content. In addition, 200 c.c. of a 25 per cent solution of glucose were given intravenously on three successive days. No digitalis was administered. Within three days the urinary output began to increase, with a corresponding decrease in the edema. During the first ten days the patient's weight was reduced from 166 to 132 pounds.

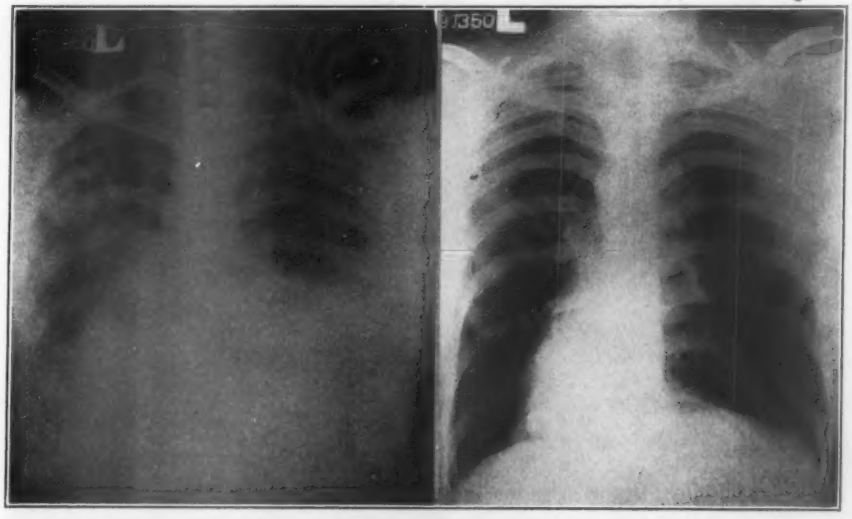

Fig. 1*A*. Fig. 1*B*.

A teleoroentgenogram made Oct. 3, 1935, the day after admission, revealed evidence of bilateral hydrothorax and passive congestion of both lungs (Fig. 1*A*); the heart was probably enlarged, but exact measurements could not be made because of the pleural effusion. The second teleoroentgenogram was made Feb. 19, 1936 (Fig. 1*B*). At this time the size of the heart was normal (Danzer ratio 0.39), and the blood pressure had fallen to 150/90. An electrocardiogram taken shortly after admission revealed an inverted T-wave in Lead I (Fig. 2), and subsequent curves which were obtained at irregular intervals also showed T-wave changes. It is significant that the T-wave abnormality which was originally present in both Leads I and II disappeared as the patient's condition improved. During the first ten days in the hospital several new hemorrhages appeared in the eyegrounds.

On Oct. 7, 1935 (the fifth hospital day), a biopsy of deltoid muscle revealed a subacute perivascular inflammation involving particularly the arterioles (Fig. 3). Another biopsy, Nov. 11, 1935, showed that the perivascular process was less severe and of a more chronic nature. A third biopsy was done Feb. 20, 1936 (Fig. 4). At

this time, five months after the acute illness, there was very slight thickening of the intima, but the inflammatory process had disappeared entirely.

CASE 2.—The patient was a white girl, 12 years of age, who was admitted to the University Hospital Feb. 3, 1937, complaining of swelling of the face and ankles, loss of appetite, and weakness. The past history was irrelevant except for the fact

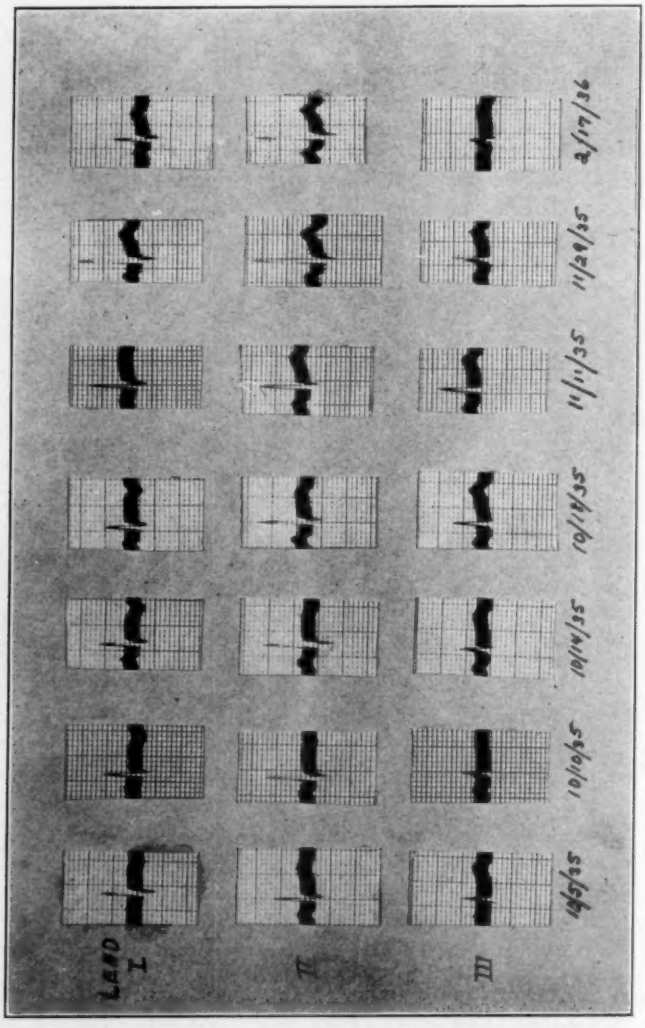

Fig. 2.

that she had had diphtheria when she was six years old. Severe epistaxis occurred at this time, but the child recovered and remained well until Christmas, 1936. At that time she contracted a cold and sore throat, followed in a few days by generalized aches and pains, dizziness, nausea, and vomiting. After one week of rest in bed she returned to school but had no appetite and complained of dizziness. One month before she came to the hospital, her hands, face, and feet began to swell. Two days before admission she had epistaxis and also expectorated some blood, and albumin and blood were found in her urine.

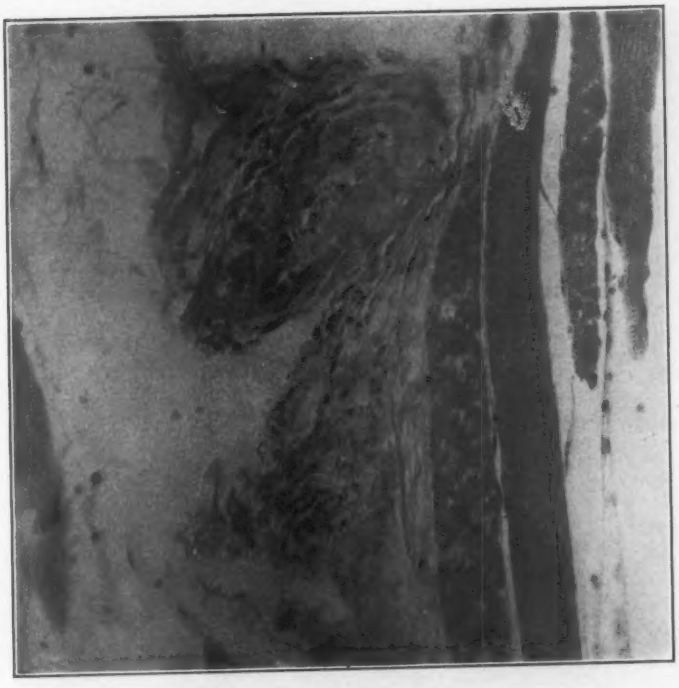

Fig. 3.

Fig. 4.

The child was quite ill and listless. Her skin was very pale. The face was puffy, and there was edema of the lower extremities. Several ecchymoses were present over the feet and ankles. The eyegrounds were normal. The pharynx was reddened and the tonsils and adenoids were greatly enlarged. Several cervical lymph nodes were palpable. A few râles were heard at the base of the left lung. The heart was definitely enlarged, with the left border at the anterior axillary line. A systolic murmur was heard at the apex and at the pulmonic area, and the pulmonic second sound was accentuated. The blood pressure was 110/65. There was tenderness over both kidneys.

The urine contained albumin (graded ++++) and blood (graded ++++, Meyer's test); its specific gravity was 1.010. The erythrocyte count was 3,000,000, the

Fig. 5.

leucocyte count 22,500, and the hemoglobin 70 per cent (Sahli). Chemical examination of the blood revealed the following: nonprotein nitrogen, 96 mg. per cent; calcium, 7.8 mg. per cent; phosphorus, 4.8 mg. per cent; total serum protein, 6.1 per cent (albumin 2.3, globulin 3.3, fibrinogen 0.5). The total amount of protein in the urine for a twenty-four-hour period was 12 gm. A blood culture remained sterile.

The rectal temperature varied from 100 to 104° F. throughout the period of observation. The patient became increasingly edematous, and the urine consistently contained large amounts of albumin and blood.

On the third hospital day gallop rhythm and pulsus alternans were discovered. A teleoroentgenogram confirmed the clinical impression that the heart was enlarged. On the seventh hospital day the blood pressure was 135/90, on the thirteenth day 300/100, and on the seventeenth day 190/80. The patient died eighteen days after admission.

Post-mortem examination revealed acute arteriolitis involving some of the vessels in practically all of the tissues of the body (skeletal muscle, brain, heart, kidneys, alimentary tract, pancreas, liver, adrenals, urinary bladder, genitals); acute glomerulonephritis; generalized edema; left ventricular hypertrophy; and necrotizing lobular pneumonia. A specimen of blood taken post mortem contained 196 mg. per cent of urea nitrogen and 9.1 mg. per cent of creatinine.

The lesion seen in a section taken from the pectoralis major is typical (Fig. 5). In many of the arterioles and smaller arteries the muscle layer was the seat of marked hyaline necrosis, and an inflammatory process, with lymphocytes, large mononuclear cells, and many polymorphonuclear leucocytes, was spreading toward the lumen. There were many areas of replacement fibrosis of the vessel wall, and

Fig. 6.

frequently the lumen was almost obliterated. The stage and degree of change within the arterioles were variable; some appeared normal, in others there was evidence of an acute process, and in still others the fibrosis and slight leucocytic infiltration were indicative of an old lesion in the stage of healing. No aneurysms or thrombi were seen. The striated muscle showed scattered areas of degeneration which were doubtless the result of the vascular lesions.

The heart weighed 260 gm. The wall of the left ventricle was 1.6 cm. thick, whereas that of the right measured only 4 to 6 mm. The coronary arteries were collapsed, but patent. No areas of scarring were found in the myocardium; the muscle was firm and pale. The valves were normal. Of four sections taken from the myocardium, three showed only slight vascular disease, but in the fourth it was severe (Fig. 6). The walls of several coronary arteries were greatly thickened, their lumina were decreased in caliber, and the muscle layer had been replaced by fibrous

tissue and infiltrated with leucocytes, including a few eosinophiles. The small vessels within the myocardium were similarly altered, but only one showed the acute stage of arteritis seen in the arterioles of the pectoral muscle.

SUMMARY

Both of these patients presented the clinical manifestations of acute nephritis with cardiac failure. The second patient had a widespread inflammatory lesion of the arterioles, including those of the heart, but the glomerular damage was minimal. Judging from the arteriolar changes in the straited muscle, the hemorrhages in the ocular fundi, the hematuria, hypertension, and cardiac failure, it is probable that the first patient had the same disease as the second. We believe that the histologic evidence of widespread vascular disease in these two patients warrants consideration of the following two possibilities: (1) that acute nephritis is part of a widespread vascular disease which is occasionally severe enough to be called panarteriolitis, or (2) that many patients who seem to have acute nephritis with cardiac failure actually have panarteriolitis with involvement of the vessels of the myocardium.

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A NEW SENSITIVE RECORDING OSCILLOMETER*

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THE potential usefulness of oscillometry in the investigation of peripheral vascular phenomena is only partially realized with the oscillometers now in use. These instruments are so insensitive as to permit measurements only in those parts of the extremities which are traversed by arteries of considerable size, and the measurements so obtained reflect chiefly the condition of these relatively large vessels. It is well known, however, that circulation through the small vessels of the arterial system, as estimated from the appearance and functional capacity of an extremity, may be surprisingly efficient in spite of strikingly diminished oscillometric readings. Conversely, the patency of the peripheral arterioles may be greatly reduced without a corresponding decrease in oscillometric measurements as they are usually made. This is a common observation during the spasms of Raynaud's disease. It is clear that the data obtainable from the leg or arm are inadequate for estimating the status of the digits.

The purpose of the present communication is to describe a new type of oscillometer suitable for making precise measurements directly upon the toes and finger tips. The oscillations recorded in these locations necessarily reflect the pulsation of small vessels, since no large vessels are found there, and for this reason the magnitude of oscillation is greatly influenced by the state of peripheral vascular tonus. It is probable also that local blood pressure may be estimated from the tracings in a manner analogous to the familiar use of the ordinary oscillometer for this purpose, but this has not been checked by direct intravascular pressure measurements. Similarly, the instrument may be used to measure the blood pressure of small laboratory animals.

The oscillometer is shown in Fig. 1, and its construction is indicated schematically in Fig. 2. Vascular pulsations are transmitted from the cuff *A* to the membrane *B* through an incompressible fluid medium (alcohol), in which a distensible tambour *C* is interposed. This tambour permits the cuff pressure to be varied at will by means of the compression bulb *D* and tank *E* while the mean pressure at the membrane is maintained at zero with the leveling cylinder *F*. In each instance the connection to the pressure-regulating device is made through a long length of coiled metal tubing *G, H,* in order to increase the inertia of these parts of the fluid system. The membrane *B* is in close proximity to a vent *J*, through which compressed air flows under constant pressure. Movements of the membrane alter the clearance at the

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vent and so regulate the escape of air through it. The resulting fluctuations of pressure within the chamber *K* are recorded by the tambour *L*. The mean cuff pressure is recorded by the tambour *M*, and in order to permit the use of two cuffs an outlet N is provided for connection of the proximal cuff *O*. By these means the vascular pulsations actuate the membrane *B*, which in turn regulates the pressure in the chamber *K* and so produces enormously amplified oscillations of the recording tambour *L*. Since *L* operates under a relatively high pressure there is ample power to operate the recording mechanism. The oscillations may be still further amplified by connecting, in place of the tambour *L*, another diaphragm *P* whose movements regulate the escape of air from a second vent *Q*. This vent is then connected to the recording tambour *L*. The change from first to second stages of amplification is effected by means of the valves *R* and *S*.

The cuff *A* is made of reinforced latex rubber, thin and yielding at its inner surface and sides, but relatively inelastic at its outer surface. It is 3 cm. wide and 10 cm. long with a natural curvature adapting it to the digit. In order to minimize

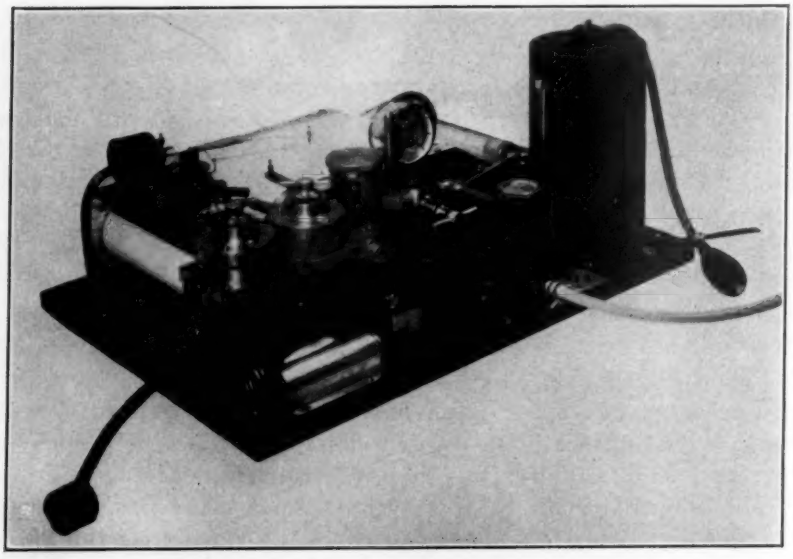

Fig. 1.—The new oscillometer.

damping of vascular pulsations, the cuff is connected to the amplifier through a relatively rigid short rubber tube. The cuff should be at the same level as the fluid in tank *E* in order to avoid a hydrostatic error in recording the mean cuff pressure. Tambour *C* is fashioned from a metal sylphon bellows 1⅜ inches in diameter.* Membrane *B* is 1.25 cm. in diameter, is made of thin rubber dam and is under very little tension. A thin metal disk three-quarters the diameter of the membrane is cemented to the central portion of its upper surface. This furnishes a smooth flat contact surface for the vent.

It is apparent that for maximum sensitivity of the machine, the transmission of pulsatile forces through the tubes *H* and *G* must be effectively damped. If the tubes are too short they do not introduce sufficient inertia to accomplish this result. On the other hand, excessively long tubes produce an undesirable lag in reaching a pressure equilibrium. As a compromise, *H* is about 2 meters long and *G* slightly longer, ⅛ inch copper tubing being used for both. A more perfect but less con-

*Manufactured by the Fulton Sylphon Company.

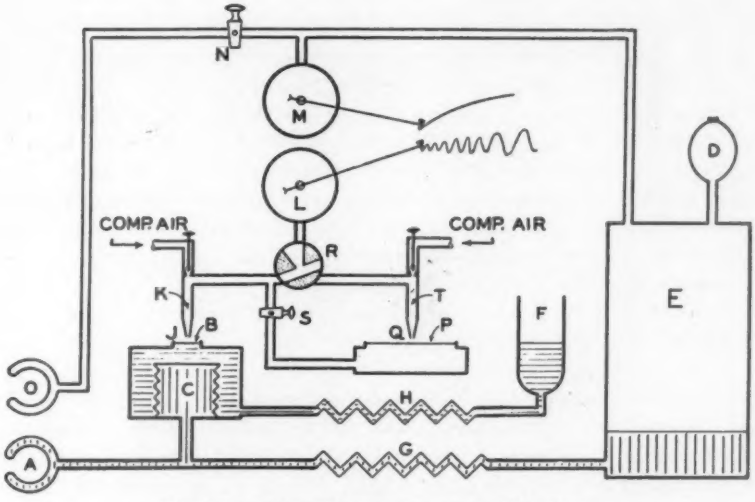

Fig. 2.—Schematic drawing of oscillometer.

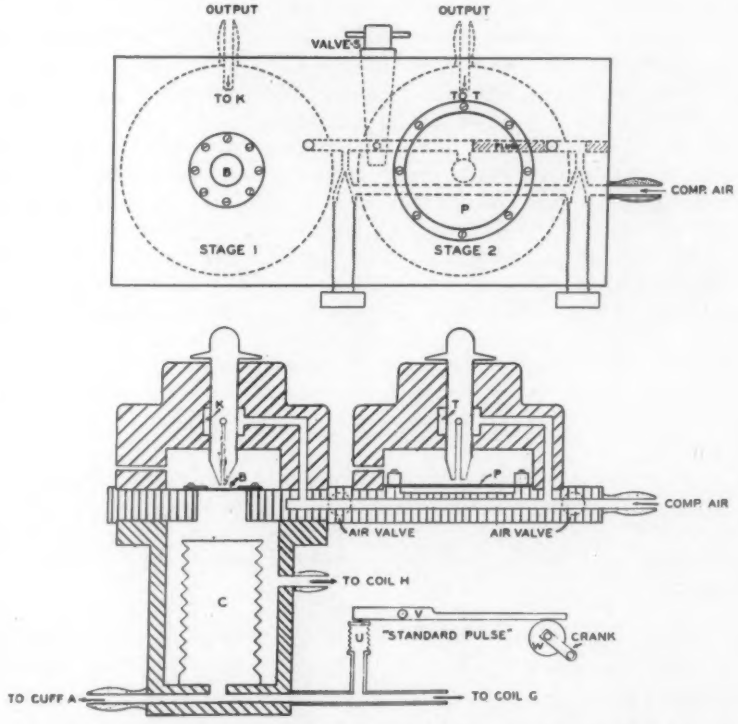

Fig. 3.—The "standard pulse" and two-stage amplifying unit.

venient arrangement utilizes very long tubes with by-pass valves to be opened while the mean cuff pressure is changed. The cylinder *F* is 5 cm. wide, so that the level of fluid within it changes but little as a result of changes in the distention of tambour *C*. A finely threaded, calibrated screw regulates the clearance of vent *J*, whose aperture at the tip is 0.1 cm. in diameter. The tambour *L* is a modified Tycos sphygmomanometer. A rod is soldered to the large gear within and projects through a slot cut in the side of the case. Hinged to this rod is a long, metal, capillary-tube pen which dips into an inkwell mounted above the gear. The pen swings in a horizontal plane over the table of a motor-driven paper-feeding device. The tambour operates at a mean pressure of about 170 mm. of mercury. Tambour *M* is a pressure meter of 0 to 500 mm. of mercury range.*

Compressed air which furnishes the power for driving the recording tambour *L* is first passed through a filter and Hoke "Pheonix" pressure regulating valve, which are not indicated on the diagram. The rate of air flow into the chambers *K* and *T* is regulated by calibrated needle valves. In order to be sure that the rate of inflow will be relatively little influenced by the pressure changes occurring within the chambers during the operation of the oscillometer, a line pressure of 30 pounds per square inch is employed. The membrane *P* is 4.2 cm. in diameter and is made of latex rubber, 0.2 cm. thick, in which is imbedded a metal disk (1.8 cm. in diameter) to keep the central portion flat. Another small thin disk is cemented to its upper surface for contact with the vent *Q*, whose aperture is 0.225 cm. in diameter at the tip. The liquid in the fluid system communicating with the cuff *A* is 70 per cent alcohol, which was selected because of its low viscosity and specific gravity. Water is used in the remainder of the fluid system because of the destructive action of alcohol upon the membrane *B*.

The selection of a practical unit for expressing oscillometric measurements depends upon the characteristics of the instrument employed. Units of volume or of pressure are both unsuitable since the operation of the oscillometer is neither isobaric nor isometric, but involves simultaneous changes in both pressure and volume, and hence measures a composite effect. Moreover, in the instrument here described, the magnitude of oscillation is somewhat dependent upon the pulse rate and also upon minor changes in the adjustment of the apparatus, which may slightly alter its sensitivity. For these reasons the instrument is calibrated in terms of a reproducible arbitrary unit, or "standard pulse." This device produces impulses of uniform magnitude and may be operated at the same rate as the pulse, thus automatically correcting for this variant. In practice the standard pulse is always so operated at the end of a determination, and the magnitude of vascular oscillations may then be expressed in terms of the standard, which facilitates comparison with other determinations.

The standard pulse machine, represented in Fig. 3, consists essentially of a small metal tambour *U* intermittently compressed by means of a lever *V* and slightly eccentric cam *W* so as to displace 0.005 c.c. with each stroke. In the same figure the two-stage amplifying unit is illustrated in detail to indicate the relationship of the various parts.

The sensitivity of the oscillometer and the appearance of records made with it are illustrated by Fig. 4, 5, and 6. Fig. 4 is the oscillogram of the distal phalanx of the index finger of a normal subject, made with the single-cuff technique and one stage of amplification. The tracing is read from right to left, and the falling line indicates the mean cuff

*Manufactured by the Bristol Company.

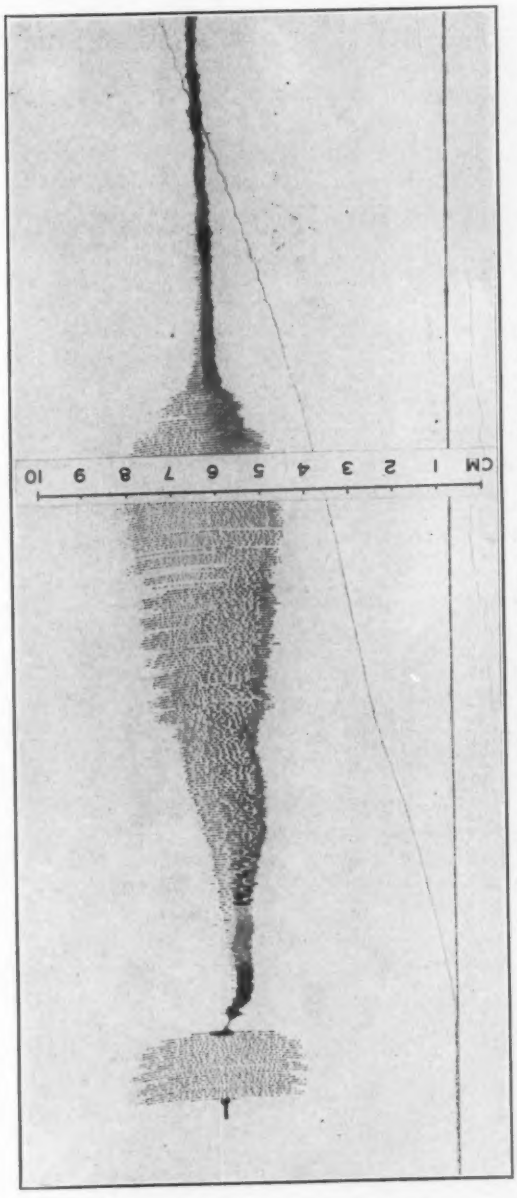

Fig. 4.—Oscillogram of a normal finger tip, first stage.

pressure. The small oscillations of approximately equal size at the extreme right are supramaximal. The tracing at the extreme left is the standard pulse curve. It may be seen that the largest vascular pulsation

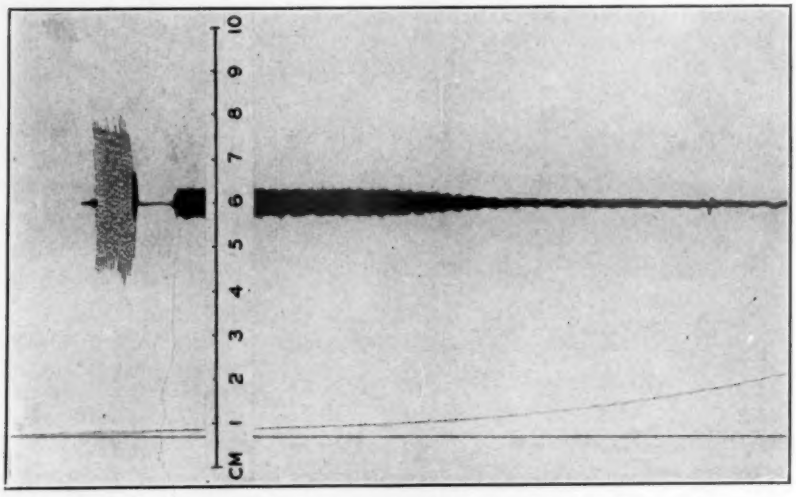

Fig. 5.—First stage oscillogram of a toe, in a patient with arteriosclerotic peripheral vascular disease.

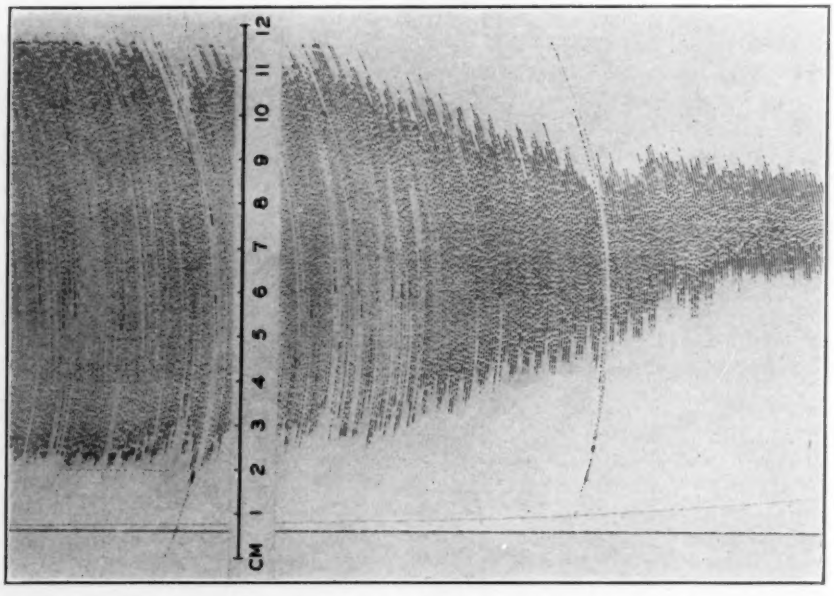

Fig. 6.—Second stage oscillogram of the same toe as that from which Fig. 5 was obtained.

is 3.7 cm. long, or approximately 0.9 standard pulse units. Using the criteria generally employed for estimation of blood pressure from oscillometric measurements, the local blood pressure in this instance is

115/65. The oscillations shown here are of the usual magnitude for a finger tip and are by no means the largest observed. For pulsations of this size the second stage of amplification is not used because the oscillations then greatly exceed the range of the recording tambour.

Fig. 5 is the oscillogram of the great toe of a 54-year-old diabetic patient with arteriosclerotic peripheral vascular disease whose oscillometric indices as measured with the Pachon oscillometer were 2.0 at the thigh, 0.5 below the knee, and 0.1 at the ankle. The tracing in Fig. 5 was made with one stage of amplification at a room temperature of 75° F., and the mean cuff pressure and standard pulse curves are shown as in the preceding figure. The oscillometric index is 0.2 standard pulse units and the local blood pressure is notably low. Immediately after making the record shown in Fig. 5 another oscillogram was made on the same subject, using the second stage of amplification under conditions otherwise identical. A portion of this record is shown in Fig. 6. The largest oscillations represent a full scale deflection of the instrument.

The instrument may be used for measuring blood pressure in dogs and rabbits. Rarely, with a suitable cuff, vascular pulsations may be detected in the rat's tail, but the tracing is generally obscured by respiratory and other extraneous movements.

SUMMARY

A sensitive recording oscillometer suitable for precise measurement of the vascular pulsations in the toes and finger tips of man is described. The instrument is also useful for measuring blood pressure in the limbs of small laboratory animals. The use of a standard pulse eliminates errors inherent in the instrument and permits the pulsations to be expressed in terms of the standard pulse.

Department of Clinical Reports

AURICULOVENTRICULAR DISSOCIATION FOLLOWING SCARLET FEVER*

Report of a Case

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AURICULOVENTRICULAR dissociation as a sequela of scarlet fever has hitherto not been recorded so far as I can determine. Shookoff and Toran,[1] in 1931, could not demonstrate a prolongation of the P-R interval in an electrocardiographic study of a series of scarlet fever patients. On the other hand, Wichstrom,[2] in 1933, observed prolongation of the auriculoventricular conduction time beyond 0.2 sec. in five of a group of 100 scarlet fever patients. Berger and Olloz,[3] in 1934, studied sixty-six scarlet fever patients clinically and electrocardiographically and observed electrocardiographic evidence of myocarditis in four of these, but no evidence of complete heart block. The studies of Faulkner, Place, and Ohler[4] on 171 scarlet fever patients revealed abnormal electrocardiograms in eleven individuals, an incidence of 6 per cent. In five patients the abnormalities consisted merely of prolongation of the P-R interval beyond 0.2 sec. Seventy-five per cent of the patients who developed abnormal electrocardiograms were between four and sixteen years of age. The severity of the illness had no influence on the degree of electrocardiographic changes. None of the abnormalities was observed prior to the thirteenth day; the majority of the abnormal records were grouped between the nineteenth and thirty-fourth days.

The likelihood of pathologic involvement of the heart, including the conduction system, in patients with scarlet fever is emphasized by Brody and Smith,[5] who found lesions of varying severity in over 90 per cent of the cases which they studied.

CASE REPORT

R. N., a boy 18 years of age, entered the Jewish Hospital June 10, 1936, because of precordial distress, dizziness, and occasional unconsciousness.

The past medical history was negative except for measles, mumps, chicken pox, grippe, and tonsillitis.

The present illness dated back to April 4, 1935, when the patient was admitted to the Philadelphia Hospital for Contagious Diseases on the fourth day of an

*From the Medical Service, Jewish Hospital, Philadelphia.
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attack of scarlet fever. At that time his temperature was 102° F. The pulse rate was 108, and the respiratory rate, 24 per minute. The scarlet fever was of average severity. Examination of the patient's heart was reported as showing nothing abnormal aside from the accelerated rate. On April 5 the patient's pulse rate was 116, on April 7, 74; and April 9, 72 beats per minute, and the temperature was normal on the latter date.

On April 18, the eighteenth day of the illness, the pulse rate was reported as 50 per minute and then fluctuated from 50 to 60 per minute until the twenty-third day of the disease, when it rose to 80 per minute. On April 29, 1935, a systolic murmur was audible at the apex of the heart. On May 2, 1935, the patient was discharged from the Philadelphia Hospital for Contagious Diseases, the final notes

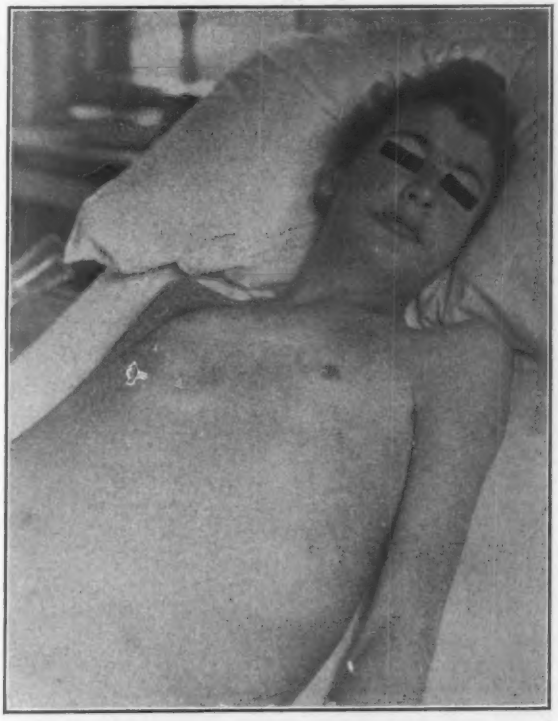

Fig. 1.—Patient in stage of decompensation. Marked cyanosis.

stating that there were no abnormal cardiac findings, and that the heart rate was averaging 70 per minute. Electrocardiographic studies were not made during the foregoing period.

Fatigue was an annoying symptom during the subsequent months, and, although the patient returned to school in the fall of 1935, he never felt quite well.

In January, 1936, he had several attacks of dizziness, blurred vision, and dyspnea. In one of the attacks he was quite alarmed about severe precordial distress. On March 25, 1936, and again on May 23, 1936, similar attacks occurred, and, in addition, were accompanied by brief periods of unconsciousness (Adams-Stokes syndrome).

On admission to the hospital June 10, 1936, the patient was fairly well nourished, dyspneic, and cyanotic. The jugular veins were engorged. The size of the heart was within normal limits. A diffuse cardiac impulse was visible in the 3rd, 4th and

5th left intercostal spaces. On auscultation the heart sounds were impaired. The blood pressure was 110/70. Otherwise the examination was negative.

On July 10, one month after admission to the hospital, the patient, while in bed, had a syncopal attack during which he became cold and cyanotic. His cardiac

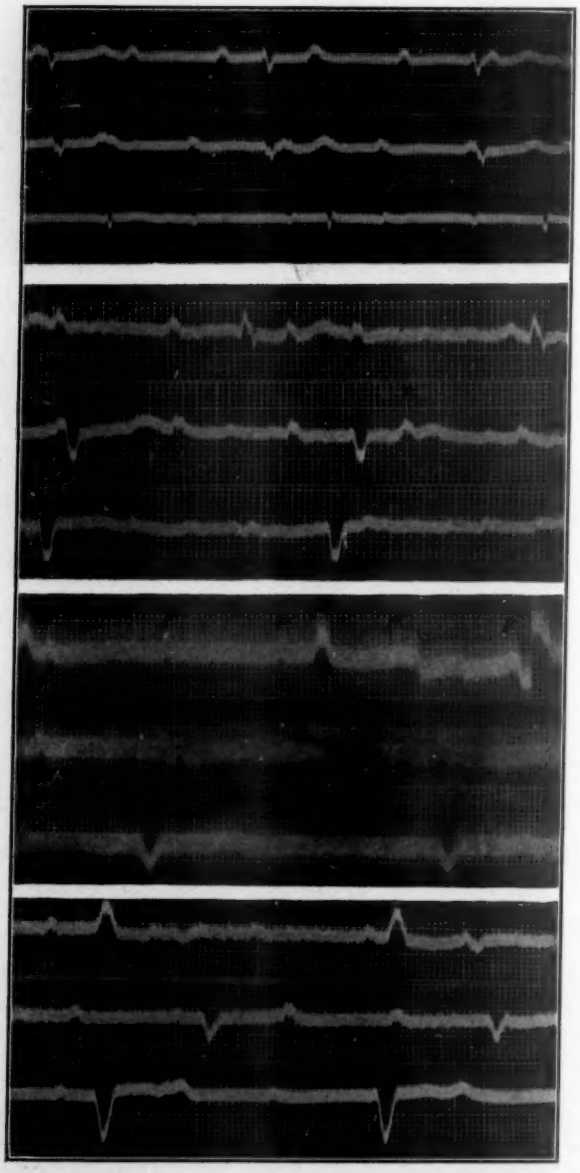

Fig. 2.—*A*, electrocardiogram taken Aug. 7, 1936. Auricular rate, 72; ventricular rate, 32. Complete A-V dissociation.

B, record taken June 11, 1937. Auricular rate, 83; ventricular rate, 33. Complete A-V dissociation.

C, Electrocardiogram made Jan. 12, 1938. Auricular rate, 72; ventricular rate, 28-30. Complete A-V dissociation. Arborization block.

D, Record taken May 5, 1938. Auricular rate, 83; ventricular rate, 30. Complete A-V dissociation. Left bundle branch block. Severe myocardial disease.

rate was noted to be 40 per minute. Electrocardiographic study on July 11 indicated complete heart block with an auricular rate of 107 and ventricular rate of 41 per minute.

Cardiac decompensation followed and has persisted despite the use of all known therapeutic measures. The cyanosis (Fig. 1) has always been marked and jugular pulsation can be noted frequently. Cardiac hypertrophy developed slowly.

On auscultation one can frequently hear the auricular sounds over the 3rd and 4th left interspaces, in addition to the changing quality and intensity of the first cardiac sound. The cardiac rate ranges from 28 to 40 per minute. The systolic blood pressure varies between 90 and 100 mm. Hg and the diastolic, between 60 and 75. Repeated electrocardiograms during 1936-1937-1938, several of which are shown in Fig. 2, all indicated severe myocardial damage and complete heart block.

Paracentesis thoracis has been necessary eleven times since Sept. 8, 1936, with removal of a total of 9825 c.c. of clear fluid; abdominal paracentesis has been performed on thirteen occasions since Oct. 31, 1936, with removal of a total of 48,012 c.c. of clear fluid; and venesection has been necessary on five occasions since Sept. 24, 1936, with removal of a total of 925 c.c. of blood.

On Jan. 20, 1938, the circulation time from arm to tongue was 42 seconds, and the ether time was 22 seconds. The venous pressure was difficult to measure.

Various other laboratory data were all essentially negative.

COMMENT

The clinical history herein presented indicates that the patient did not evidence any cardiac involvement prior to April 4, 1935, when he was admitted to the Philadelphia Hospital for Contagious Diseases during an attack of scarlet fever. Observation during the patient's stay at this hospital disclosed a bradycardia which occurred on the eighteenth day of the disease, the cardiac rate being recorded at 50 per minute and then varying from 50 to 60 per minute for five days. Later the pulse rate increased to 80 per minute, but, when the patient was discharged from the Philadelphia Hospital for Contagious Diseases, the rate was 70 per minute. The slowing of the cardiac rate to 50 per minute during the attack of scarlet fever suggests that scarlet fever was the cause of the bradycardia.

Faulkner and his co-workers[4] observed that in scarlet fever the majority of cardiac abnormalities were noted after the thirteenth day and that most of the abnormal electrocardiographic records were grouped between the eighteenth and thirty-fourth days. This patient evidenced the slow heart rate on the eighteenth day of his attack of scarlet fever.

CONCLUSION

A case of complete auriculoventricular dissociation as a sequel of scarlet fever emphasizes the importance of careful follow-up electrocardiographic studies of all individuals convalescing from the disease. Such investigations would in all probability reveal additional instances of auriculoventricular dissociation. If this proves to be the case, it would seem logical to conclude that a longer rest period for patients

recovering from scarlet fever should be prescribed. This patient, who is still under observation, has complete heart block and cardiac decompensation.

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PAROXYSMAL BUNDLE BRANCH BLOCK ASSOCIATED WITH PHYSIOLOGIC CHANGES IN A PATIENT WITH ORGANIC HEART DISEASE

Report of Case*

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RECENTLY, Comeau, Hamilton, and White[1] reported thirteen cases of paroxysmal bundle branch block associated with heart disease and collected 58 additional cases from the literature. They excluded the cases described by Wolff, Parkinson and White,[2] in which there were wide QRS complexes, short P-R intervals, and no evidence of organic heart disease. At about the same time Bishop[3] described a case of transient, recurrent bundle branch block in a patient with organic heart disease. The following is a report of an additional case.

CASE REPORT

History.—A white woman, 66 years old, was seen March 26, 1938. She complained of paroxysmal nocturnal dyspnea, orthopnea, and dyspnea on exertion, all of three months' duration. Three years previously she had begun having severe frontal and parietal headaches accompanied by visual disturbances, tinnitus, vertigo, and syncope. One year later she had a cerebral hemorrhage and left-sided hemiplegia from which she recovered in three months. There had been no edema of the ankles. The past and family histories were irrelevant.

Physical Examination.—The patient was acutely ill and markedly orthopneic. Examination of the eyegrounds showed moderate tortuosity of the retinal arteries. The jugular veins were distended with the patient in a semiupright position. The respiratory rate was increased. The percussion note was dull below the angles of the scapulae. The breath sounds were diminished in intensity at both bases and accompanied by numerous, medium, moist râles. The radial pulses were of poor quality, equal and, except for an occasional extrasystole, regular. The pulse and heart rates were 118 per minute, the blood pressure 220/160. Precordial activity was increased. The point of maximum impulse was seen and felt as a diffuse pulsation in the fifth interspace in the left anterior axillary line. The area of cardiac dullness was enlarged markedly to the right and left. The heart sounds were of poor quality, and there were no accentuations. Except for an occasional extrasystole the beating was regular. A soft untransmitted systolic murmur was present at the apex. The edge of the liver was palpable just below the costal margin and was tender. There was no ascites nor dependent edema. There was no paralysis, but residual hemiplegic signs were present on the left side.

The specific gravity of the urine was 1.026, and it contained a little albumin (+) and a few granular casts. Examination of the blood showed no significant changes; the blood Wassermann reaction was negative. The sedimentation rate was 0.7 mm. per minute.

*From the Department of Medicine, the South Bend Clinic.
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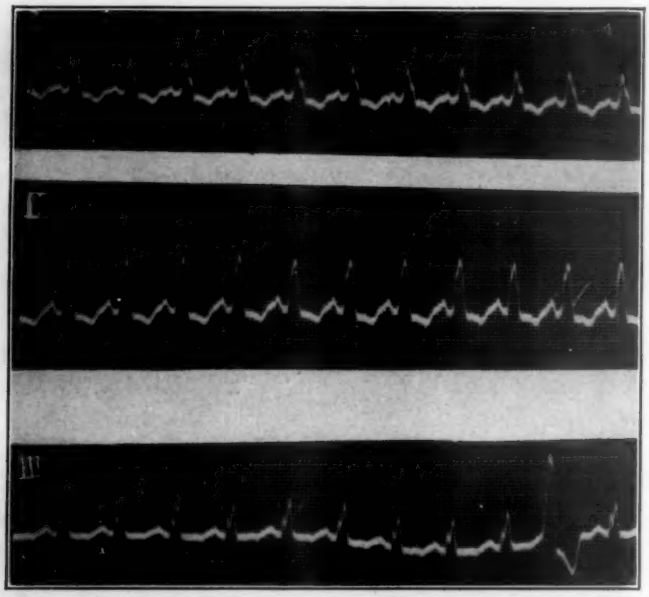

Fig. 1.—Electrocardiogram taken March 26, 1938, while patient had acute heart failure. Auricular and ventricular rates, 115. P-R interval, 0.14 sec. QRS time, 0.12 sec. Time marker, 0.20 sec. and 0.04 sec.

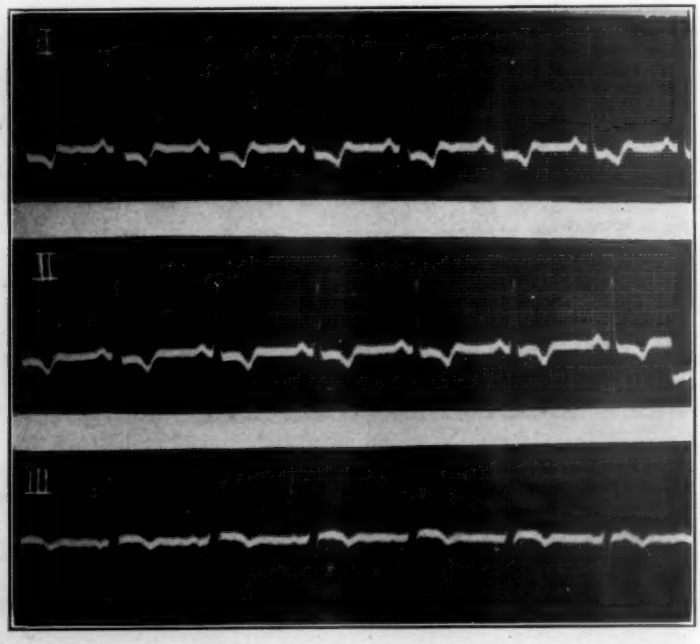

Fig. 2.—Electrocardiogram taken April 4, 1938, nine days after admission. The heart is compensated. Auricular and ventricular rates, 65. P-R interval, 0.16 sec. QRS time, 0.08 sec. Time marker, 0.20 sec. and 0.04 sec.

A teleoroentgenogram showed marked enlargement of the heart to the right and left and extensive passive hyperemia of the lungs.

An electrocardiogram (Fig. 1) showed auricular and ventricular rates of 115, a P-R interval of 0.14 sec. and a left* bundle branch block with QRS time of 0.12 sec. The T-waves were inverted with low points of origin in Leads I and II, and followed the isoelectric line in Lead III.

The diagnosis was hypertensive heart disease with cardiac enlargement and congestive failure, coronary sclerosis, left bundle branch block, and questionable coronary thrombosis.

Course.—The patient was digitalized and given the usual treatment for cardiac failure. She was discharged from the hospital April 4, nine days later, with limited cardiac reserve but no evidence of decompensation. The heart rate was 68 and the

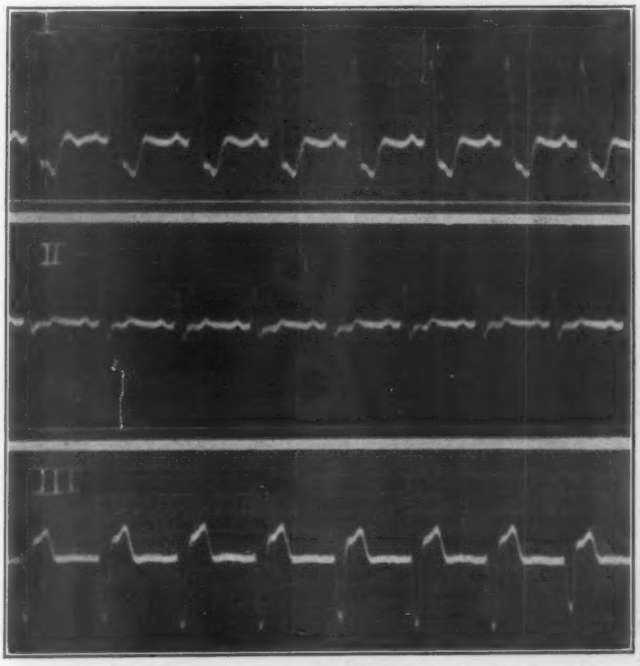

Fig. 3.—Electrocardiogram taken May 31, 1938, eight weeks after discharge. The heart is compensated. Auricular and ventricular rates, 75. P-R interval, 0.18 sec. QRS time, 0.13 sec. Time marker, 0.20 sec. and 0.04 sec.

blood pressure 208/140. The point of maximum impulse was forceful and well localized. Lateral to it was a systolic retraction. The area of cardiac dullness had diminished and the heart sounds had improved in quality. The systolic murmur at the apex had increased in intensity but was soft in quality.

An electrocardiogram (Fig. 2) taken at this time indicated that the bundle branch block had disappeared. The auricular and ventricular rates were 65, left axis deviation was present, and the voltage was high.

The patient resumed her usual activities with some restrictions and returned, May 31, eight weeks later, for re-examination. The heart was well compensated, the rate 76 and the blood pressure 224/138. An electrocardiogram (Fig. 3) indicated

*The designation of left bundle branch block accords with the terminology proposed by Wilson and his co-workers.[4]

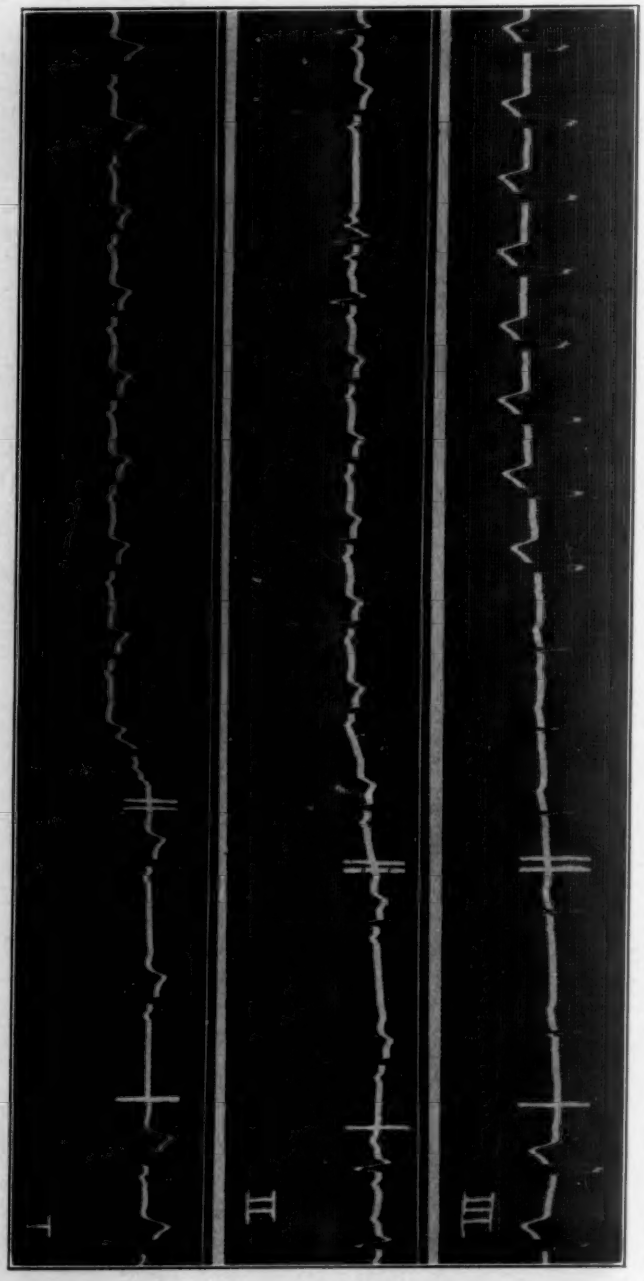

Fig. 4.—Electrocardiogram (May 31, 1938) showing the effect of carotid sinus pressure. The single vertical white line denotes application of carotid sinus pressure and the double vertical white line denotes release of carotid sinus pressure. Time marker, 0.20 sec. and 0.04 sec.

that bundle branch block had reappeared, and that the auricular and ventricular rates were 75. Fig. 4 shows the effect of carotid sinus pressure. Pressure was applied over the right carotid sinus at a time designated on the electrocardiogram by the single vertical white line. A marked slowing of the rate followed, and there was immediate disappearance of the bundle branch block. Pressure was maintained

for a period covering two ventricular contractions and then discontinued. Discontinuance of pressure is designated by the double vertical white line. At this point the heart rate began gradually to increase. Unslurred QRS complexes of normal duration continued in each lead until a certain critical heart rate was reached. This level was approximately 71 beats per minute, and whenever it was exceeded branch block was re-established. The block continued until it was again abolished by carotid sinus pressure. In Lead II of Fig. 4 there was a premature auricular contraction shortly after the re-establishment of branch block. This resulted in a partial

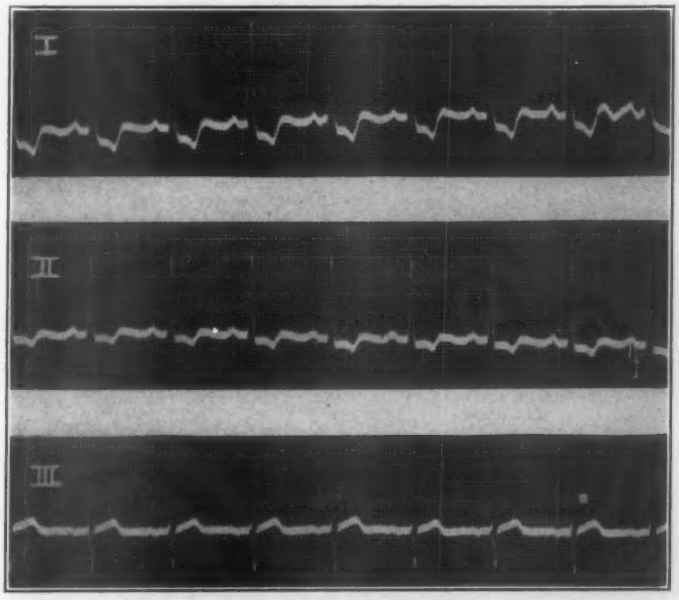

Fig. 5.—Electrocardiogram taken June 14, 1938. Auricular and ventricular rates, 79. P-R interval, 0.22 sec. QRS time, 0.07 sec. Time marker, 0.20 sec. and 0.04 sec.

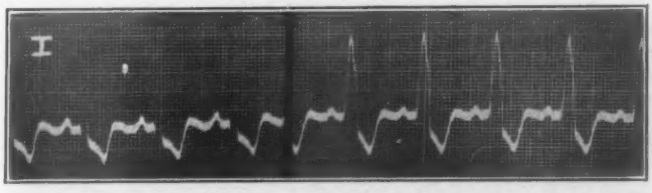

Fig. 6.—Electrocardiogram (June 14, 1938) showing the effect of exercise on intraventricular conduction. The vertical black line divides the records taken before and after exercise. Approximately three minutes elapsed between the end of exercise and the beginning of the second portion of this record. The rate before exercise, 82; three minutes after exercise, 83. P-R interval before exercise, 0.22 sec.; after exercise, 0.20 sec. QRS time before exercise, 0.07 sec.; after exercise, 0.13 sec. Time marker, 0.20 sec. and 0.04 sec.

compensatory pause, and the next QRS complex was not blocked. Those that followed indicated that branch block had been resumed.

On June 14 the patient returned. The pulse and heart rates were 78, and the blood pressure 194/130. There were, otherwise, no significant changes on physical examination.

An electrocardiogram (Fig. 5) taken on this occasion showed no bundle branch block. The QRS time was 0.07 sec., and the auricular and ventricular rates were 79. The patient was given mild exercise which caused marked dyspnea and moderate elevation in heart rate. An electrocardiogram taken immediately after exercise indicated that the rate had increased to 84 and that left bundle branch block had been re-established. After a rest period of twenty minutes a third electrocardiogram showed a rate of 79 with branch block persisting. Right carotid sinus pressure was then applied as formerly. It was followed by a reduction in heart rate and the abolition of bundle branch block. After release of pressure the rate increased gradually to 82, as shown in the first portion of Fig. 6. Bundle branch block, however, was not present. The patient then exercised, causing dyspnea out of proportion to the elevation in heart rate, which increased to 88 as counted from the radial pulse. After a rest period of approximately three minutes, the second portion of Fig. 6 was taken. The rate was now 83, with bundle branch block again present.

DISCUSSION

When this patient first came under observation the bundle branch block was thought to be the result of coronary disease and myocardial fibrosis. The T-wave changes supported this view. Later, with the return of compensation, the block disappeared. Its former presence was then attributed, in part, to anoxemia or nutritional changes in a failing, dilating heart. This explanation, however, would not account for its reappearance within eight weeks, at a time when there was no cardiac failure. Except for a moderate increase in heart rate no significant changes perceptible by physical examination had taken place during this period. The electrocardiogram showed an increase in heart rate from 65 to 75. It was then thought that the increased rate might be an additional or precipitating factor in producing branch block without necessarily invalidating the previous explanations.

Comeau and his co-workers have emphasized this point, and the reader is referred to their article[1] for a comprehensive discussion of the available case material. They call attention to experimental evidence which shows that under certain conditions conduction may be normal at low heart rates and impaired at high heart rates. From their clinical studies they were able to conclude that in some cases the inhibiting factors capable of producing branch block are not effective when the heart rate is below a certain critical level. This critical level may vary in the same individual, but, whenever it is exceeded, branch block ensues. Yater[5] has emphasized the bilateral nature of bundle branch lesions and has demonstrated that the form of the electrocardiogram depends upon which branch is the more seriously damaged. However, metabolic and physiologic factors may be superimposed, and it is not necessary to have complete block anatomically in order to produce the typical electrocardiographic picture. All that is necessary is that the total effect of the inhibiting factors in the one branch be greater than the effect of those along the other branch and in the ventricular myocardium.

In the case under discussion it is difficult to evaluate the exact roles played by the various inhibiting factors in producing branch block. The essential structural factors are myocardial fibrosis and chronic or acute coronary disease, and the physiologic factors deserving consideration are fatigue and recovery time of the conduction fibers, nutrition, oxygenation, and the calcium and potassium metabolism of cardiac tissue. Vagal influences apparently function through the medium of a reduced heart rate, while vasomotor changes do not appear to play a role.

Although the underyling lesion is anatomic in nature, the electrocardiographic picture varies with the physiologic load which the heart is carrying. Under certain conditions a specific relationship exists between the heart rate and the type of intraventricular conduction. In Fig. 4 the release of carotid sinus pressure was followed in each lead by a gradual increase in heart rate until a certain critical threshold was exceeded. Once this threshold was exceeded, branch block ensued. There were no transitional complexes, and the block persisted until again abolished by carotid sinus pressure. The only exception occurred in Lead II of Fig. 4, and served to substantiate the apparent explanation. A premature auricular contraction which produced an incomplete compensatory pause thereby reduced the heart rate sufficiently to permit the appearance of a single unblocked QRS complex. In the succeeding contractions branch block was resumed.

On a subsequent visit the patient had reverted to unblocked intraventricular conduction. Light exercise converted this to blocked conduction which persisted until unblocked conduction was again induced by carotid sinus pressure. On this occasion it was not possible to establish such a close correlation between the heart rate and the type of conduction. Fig. 6 shows both types of conduction at practically the same heart rate. This would seem to indicate that factors other than the heart rate were playing a role in determining the balance between blocked and unblocked conduction. The fact that exercise caused dyspnea out of proportion to the elevation in heart rate is evidence that anoxemia might have been a factor. Conversely, it is known that the inhalation of oxygen[6] will, in certain instances, abolish paroxysmal bundle branch block in organic heart disease.

SUMMARY AND CONCLUSIONS

While it is not possible to draw specific conclusions from the data obtained in this case, certain facts stand out. The essential pathologic changes were hypertensive heart disease with congestive failure and subsequent compensation. In addition, there was electrocardiographic evidence of chronic or acute coronary disease and myocardial fibrosis. Finally, there was throughout the course of the acute illness as well as the convalescence a paroxysmal left bundle branch block which depended on changes in cardiac activity. Most striking of these was the relation-

ship between intraventricular conduction and the heart rate. This relationship, however, was not invariable, and therefore it appears that other physiologic factors, such as anoxemia, were playing a role.

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OBSERVATIONS ON THE MECHANISM OF THE DYING HEART IN A PATIENT WITH VENTRICULAR TACHYCARDIA*

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THESE observations are of unusual interest because they reveal for the first time that with acute coronary thrombosis and ventricular tachycardia the mechanism of the dying heart may be ventricular standstill instead of ventricular fibrillation.

REPORT OF CASE

J. B. G. (Case 51629), a man, aged 52 years, was admitted to the Bayonne Hospital Nov. 24, 1937, and died at 1:45 P.M. on Nov. 25, 1937.

The patient worked as a clerk and was perfectly well until two weeks prior to his admission to the hospital, when he began to complain of uneasiness in the precordial and parasternal regions. One week later he experienced a severe retrosternal pain accompanied by nausea and vomiting and profuse perspiration. Within eighteen hours he was relieved of these symptoms, but he felt too weak to continue work and remained at home. On the evening of Nov. 23, 1937, two days prior to his death, he experienced an attack of breathlessness accompanied by perspiration, anxiety, and precordial distress. He coughed throughout that night, and because of the increasing severity of symptoms he sought hospital care.

Physical examination on admission to the hospital revealed a plethoric, breathless, and orthopneic individual who appeared acutely ill. Large beads of perspiration covered his forehead. His skin was moist, cold, and clammy. His pulse was rapid and feeble. He complained of severe substernal distress, and he felt nauseated. His heart sounds were barely audible at the apex, and his heart rate averaged between 180 and 200 beats per minute. The blood pressure was 84/70. The lungs contained moisture, but the liver and spleen were not palpable.

Morphine was administered in adequate doses and 3 grains of quinidine sulfate were given as soon as the heart rate was found to be accelerated. Because of the increasingly intense cyanosis and breathlessness it was deemed advisable to place him in an oxygen tent, which made him distinctly more comfortable. The quinidine sulfate was continued every hour throughout his stay in the hospital, and the dose was increased to 5 grains when it became apparent that he could tolerate that amount. Fourteen hours after admission his heart rate slowed to 68 beats per minute, but within the next hour ventricular tachycardia returned and persisted until death.

DESCRIPTION OF THE CARDIAC MECHANISM

On Nov. 24, 1937, when his heart rate was discovered to be rapid, the electrocardiogram showed a tachycardia of 187 beats per minute with markedly widened ventricular complexes which were uniform in character from beat to beat (Fig. 1). All of these beats produced audible sounds at the apical region of the heart, as well as palpable pulses. The heart rate was slower on the following day, and, very likely as a result of giving quinidine, the ventricles averaged 150 beats per minute, but no evidence of auricular activity could be made out (Fig. 2). At this time he was semicomatose and began to show signs at the bases posteriorly of consolidation of both lungs. His condition became progressively worse, and on Nov. 25, 1937,

*From the Cardiographic Laboratories of the Bayonne and Montefiore Hospitals.
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at 12:40 P.M., when his respirations were 36 per minute and he was in deep coma, he was placed in the electrocardiographic circuit. Tracings were taken intermittently until about twenty-five minutes before death, after which the recording was continuous until all electrical activity ceased.

Ten minutes before his respirations stopped the ventricular rate was variable, averaging 150 beats per minute (Fig. 3), and the ventricular complexes were of lower voltage and wider than the previous ones. When the heart rate increased to 200 beats per minute the voltage of the ventricular complexes was unusually low. In these records evidence of definite auricular activity could well be discerned. Both the auricles and ventricles became slower until the tachycardia was ended by a long postundulatory pause (Fig. 4*A*) of 1 minute and 80 seconds.

In the next few minutes the heart rate averaged 41 beats per minute (Fig. 5*A*). Auricular activity could be made out only rarely, and now the ventricular complexes were wide and bizarre. Shortly the rate increased to 62 beats per minute, but no evidence of auricular activity could be seen (Fig. 6). Thereafter for twenty minutes the rate of the ventricles became progressively slower and the ventricular complexes smaller, until finally, approximately 28 minutes after the patient appeared to be dead, there was complete cessation of electrical activity.

DISCUSSION

There is a general belief based on very meager evidence that ventricular fibrillation is the terminal cardiac mechanism in patients with all forms of ventricular tachycardia,[1] but a search of the literature reveals only a few instances in which ventricular fibrillation was found to be the end-result of ectopic ventricular tachycardia.[2-6] Unfortunately, in none of these reports are there graphic observations of the transition between the ventricular tachycardia and the mechanism of the dying heart. It is very likely that if more records are obtained in such patients just before death, standstill of the heart will be found to be as frequent as, if not more frequent than, ventricular fibrillation.

It is well known from Gaskell's experiments[7] on the hearts of cold-blooded animals that the rapidity with which an idioventricular rhythm develops depends in part upon the rate at which the ventricles were beating previously. In studying the behavior of the ventricles when auriculoventricular dissociation was present, Erlanger and Hirschfelder[8] observed that after cessation of ventricular tachycardia produced by electrical stimulation there was a period of slow contraction of the ventricles. The duration of the "stoppage of the ventricles" was found to depend largely upon the duration of the preceding period of artificial stimulation and the rate at which the stimuli were applied, as well as upon a certain "depressed" condition of the heart at the time of stimulation. These observations were subsequently confirmed by Cushny,[9] who stated that, in addition to the rate and duration of stimulation, reduction of oxygen in the perfusing fluid, resulting in asphyxia, and diminution in the amount of the perfusing fluid at such times were probably also factors.

Both Erlanger and Hirschfelder, and Cushny noted that there were two types of ventricular bradycardia following artificial stimulation. In the first type, the first interventricular interval after cessation of

stimulation appeared to be the longest, and in the other type the successive intervals increased in length from beat to beat for several beats before acceleration began.

They further observed that the lengthening of the pauses after cessation of artificial stimulation was generally more marked and more per-

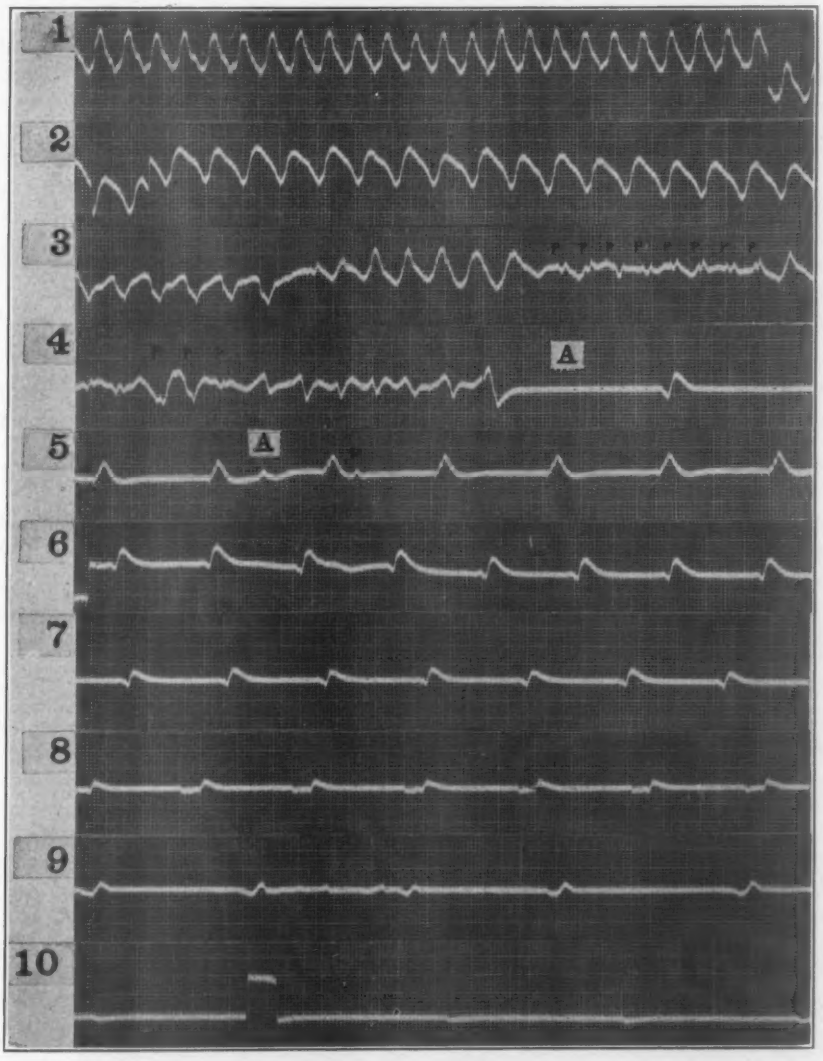

Fig. 1.—Ventricular tachycardia with a ventricular rate of 187 beats per minute.

Fig. 2.—Ventricular tachycardia with a ventricular rate of 150 beats per minute. Auricular activity cannot be made out.

Fig. 3.—Ventricular tachycardia alternating with sinus tachycardia.

Fig. 4.—Slowing of the ventricles and auricles precedes standstill of the heart (*A*).

Fig. 5.—An intermediary idioventricular rhythm with a rate of 41 and only an occasional auricular beat develops shortly after the tachycardia and three minutes after the patient appeared to be dead.

Figs. 6-10.—Variable ventricular rate with regular beating, but with no auricular activity, continues until all electrical activity ceases, twenty-eight minutes after the patient appeared to be dead.

sistent in the latter phases than in the beginning of the experiments. As the "energy" of the heart decreased, the results of the accelerated rate became greater, and a longer interval had to be allowed to obtain the return of the rate prevailing before the interference. Cushny concluded that this slow phase was not inhibitory in origin, since it occurred after, as well as before, full atropinization. He felt that the phenomenon was due to depression of stimulus formation in the ventricular pacemaker, which would be analogous to the fatigue of striated muscle, and that the contractility and excitability of the ventricles were not diminished at such times.

In ventricular tachycardia the auricles beat independently of the ventricles, but at a slower rate. It is conceivable that the rapid beating of the ventricles may progressively augment the fatigue of the ventricular pacemaker and thus lead ultimately to asystole, as in our patient. This would occur more readily if the duration of the tachycardia were such that asphyxia supervened, and in particular if there were heart muscle damage such as our patient exhibited. Theoretically, therefore, the cause of death in patients with ventricular tachycardia should be ventricular asystole, rather than fibrillation.

SUMMARY

In a 52-year-old man with acute coronary thrombosis, and an ectopic ventricular tachycardia which lasted two days, the terminal cardiac mechanism was bradycardia and ventricular standstill. The heart continued to be electrically active for twenty-eight minutes after the patient appeared to be dead. The tachycardia was ended by a long postundulatory pause; thereafter the ventricular rate was variable and auricular contractions were absent until the heart stopped completely. It is very likely that in such patients ventricular standstill is the mechanism of the dying heart as frequently as ventricular fibrillation.

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FUNCTIONAL COR BIATRIATUM TRILOCULARE*

Report of a Case With Malposed Ventricular Septum and Normal Position of the Great Vessels: A Duplicate of the Holmes Heart

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S. H. Gray, M.D.
St. Louis, Mo.

HOLMES,[1] the first Dean of McGill Medical School and one of the earliest leaders in American medicine, described, in 1824, a case of cor biatriatum triloculare with the pulmonary artery and aorta in normal relationship. Neither has Abbott,[2, 3, 4] nor have we, been able to find another reported case that is similar to this heretofore unique heart. We believe that the following case presents a duplicate of the Holmes heart.

CASE REPORT

A white girl, 14 years old, entered the Jewish Hospital Sept. 3, 1937, complaining of headache and stiff neck.

Family History.—The family history was essentially negative.

Past History.—Rapid breathing was noted shortly after birth and this persisted. A thundering precordial murmur was heard by the father, a physician, during the first week of life, and cyanosis was first noted shortly afterward. Clubbing of the fingers and toes became noticeable between the second and third years. The patient was always somewhat undernourished and undersized; otherwise, the developmental history was normal. Her general health had been good, but between the ages of 8 and 10 she had uncomplicated measles and varicella, and there had been occasional upper respiratory tract infections. There was never anything to suggest chorea, rheumatic fever, or endocarditis. Catamenia never occurred. She weighed 82 pounds at the onset of the present illness. The patient was never subjected to electrocardiographic or radiographic study.

Present Illness.—One week prior to admission the patient returned from her vacation, during which she was in good health, although on her trip home it was noted that she was less alert than usual. The following day she had a temperature of 100° F. and complained of a slight headache. Her apathy continued, although when aroused the patient displayed her usual keenness. Three days prior to entry the patient began to vomit and continued to do so several times daily. On the day before admission slight nuchal rigidity, hyperactive tendon reflexes, and poorly sustained right and left ankle clonus were found.

Physical Examination.—Examination revealed a somewhat underdeveloped, but fairly well-nourished, 14-year-old white girl. There was a suffused cyanosis of the entire skin, especially pronounced in the markedly clubbed fingers and toes. The sclerae were injected. The throat was negative except for a cyanotic hue. The heart was considerably enlarged to the left and to the right; a loud blowing systolic murmur was audible over the entire precordium, but was heard best along the left sternal border. The first heart sound was largely replaced by the murmur; the second sound was fairly loud. There was no diastolic murmur or thrill. The

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blood pressure was 108/80. The arteries were readily compressible. The lungs were not demonstrably abnormal. The abdominal examination was negative. There was no edema. Neurological examination revealed that the child was slightly irritable and apprehensive. Examination of the cranial, motor, and sensory nerves revealed no abnormalities. Ophthalmoscopic examination revealed cyanotic discs without papilledema. Nuchal rigidity was present, as were the Brudzinski and Kernig signs. The deep tendon reflexes were equal and active. The right ankle exhibited a transient clonus. There were no abnormal plantar reflexes.

Clinical Diagnoses.—It was thought that the patient had congenital heart disease, probably a defective intraventricular septum, together with meningitis, encephalitis, or even poliomyelitis.

Summary of the Clinical Course.—The temperature ranged between 99° and 104° F., varying about 1° during each day. The respirations, 22 to 40 per minute, were generally regular except for some periods of apnea in the latter days of the illness. The pulse was full, bounding, and not unusually rapid at the onset. Its rate gradually rose during the last two weeks of the illness and then remained between 130 and 140 per minute. Pathologic reflexes were frequently present, but, like the other neurological signs, were evanescent. Nuchal rigidity, an almost constant finding, varied in degree; the patient not infrequently revealed marked opisthotonus. Irritability and occipital headache were fairly constant. Clarity of the sensorium alternated with brief periods of semistupor. During the last few days isolated twitchings of various muscles occurred. A deep mulberry cyanosis, present at all times prior to the illness, varied throughout, being at first aggravated by sulfanilamide therapy and later apparently lessened by secondary anemia. At no time during the course of the illness were any significant changes noted in the heart, and only once, followed the first transfusion, were a few moist râles found at the bases of the lungs. The abdomen remained negative. Brief periods of nausea and vomiting occurred, the vomiting at times being mildly projectile. All therapy was essentially without effect and the patient grew progressively worse. Death occurred early on the twenty-seventh hospital day.

Summary of Laboratory Findings.—The spinal fluid was always cloudy and frequently bloody; the cell count ranged between 1500 and 11,000, with polymorphonuclear cells predominating; the total protein ranged between 78 and 216 mg. per cent and the sugar between 10 and 47 mg. per cent; repeated cultures of the spinal fluid by anaerobic and aerobic methods were negative. The leucocyte count ranged between 12,000 and 22,000. The erythrocyte count fell from 8,890,000 to 4,880,000, and the hemoglobin from 170 to 107 per cent (28.9 to 18.2 gm. per cent). The differential leucocyte count showed a persistent shift to the left with the stab forms ranging from 3 to 10 per cent and the polymorphonuclears from 78 to 90 per cent. The urine occasionally contained acetone and hyaline and granular casts.

Autopsy.—Post-mortem examination led to the following diagnoses: (1) Cor biatriatum triloculare (Holmes type); (2) anomalous insertion of the first, second, and third right intercostal veins into right pulmonary vein; (3) intraventricular (cerebral) abscess with ependymitis of the right lateral ventricle; (4) renal infarction; (5) thromboses of branches of the renal arteries; (6) hyperplasia of the erythroblastic tissue of the bone marrow; (7) multiple capillary thrombi of lungs and kidneys.

The heart lay in a horizontal position. The superior vena cava, which was formed by the jugular, the right azygos, and the subclavian veins, was greatly distended. The largest vein was the left subclavian. The first, second, and third intercostal veins entered the pulmonary vein on the right. These veins lay behind the azygos.

Fig. 1.—Common ventricle from the posterior aspect (four-fifths actual size). Key: *A*, aorta; *B*, aortic valve; *C*, interventricular ostium; *D*, common ventricle; *E*, mitral valve; *F*, papillary muscle between A-V valves; *G*, tricuspid valve.

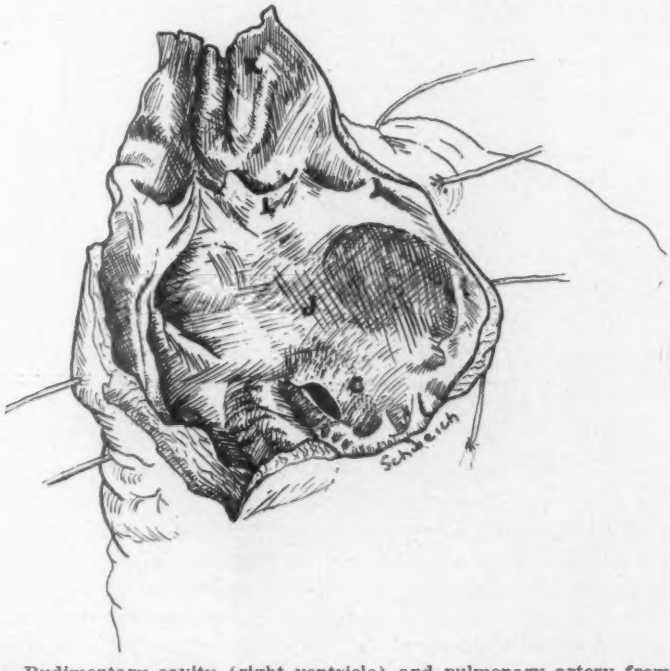

Fig. 2.—Rudimentary cavity (right ventricle) and pulmonary artery from anterior aspect (actual size). Key: *C*, interventricular ostium; *I*, pulmonary valve; *J*, rudimentary cavity (right ventricle); *K*, pulmonary artery.

The heart was broad at the base; it measured 8 cm. from the auriculoventricular groove to the apex. The greatest diameter across the ventricles was 7.5. The apex was blunt and rounded. The surface of the heart presented nothing unusual except for its ovoid shape and a rather marked fullness and tortuosity of the veins of the coronary tree.

The right auricle was moderately dilated and considerably hypertrophied. The venous trunks entered both auricles normally. The interauricular septum was very well developed. The foramen ovale consisted of two dense, broadly overlapping septa of auricular tissue between which a probe could be passed in a posterior

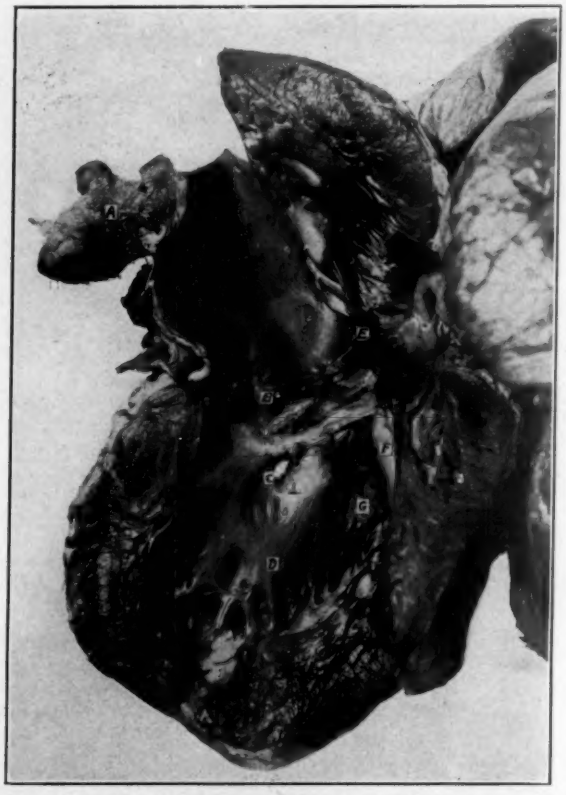

Fig. 3.—Common ventricle from the posterior aspect. Key: *A*, aorta; *B*, aortic valve; *C*, interventricular ostium; *D*, common ventricle; *E*, mitral valve; *F*, papillary muscle between A-V valves; *G*, tricuspid valve.

direction from right to left. The right auricle led into a large, thick-walled ventricle into which the left auricle also emptied. The left auricle presented no abnormality.

The common ventricle had four openings:

1. The tricuspid, communicating with the right auricle.
2. The mitral, communicating with the left auricle.
3. The aortic ostium, which arose posteriorly and approximately in the midline. The caliber of the aorta was definitely reduced, the diameter just above the aortic sinuses being 1.2 cm., and just beyond the left subclavian, 0.9 cm.

4. A small semilunar opening 0.4 cm. below the right semilunar cusp of the aortic valve and 1 cm. below the notch separating the anterior and medial cusps of the tricuspid valve. The entrance to this opening was somewhat funnel-shaped, with an overhanging thickened muscular shelf above it and an oblique concavity sloping into it from below. The opening was approximately 0.5 cm. in length and 0.2 cm. in width.

Directly below the posterior semilunar cusp of the aortic valve was an extremely well-developed muscular cushion which separated the tricuspid from the mitral valve and projected forward at its most developed portion about 0.7 cm.

Fig. 4.—Anterior view of heart showing rudimentary cavity (right ventricle) and pulmonary artery in normal relation to the aorta. Key: *C*, interventricular ostium; *H*, right auricle; *I*, pulmonary valve; *J*, rudimentary cavity (right ventricle).

This was the only structure in the common ventricle suggestive of an interventricular septum. The wall of the common ventricle measured 1.5 cm. at its thickest portion. The papillary muscles were well-developed, more so on the left than on the right. The endocardial trabeculation appeared about as it would in the average heart.

The semilunar ostium led anteriorly into a smaller chamber lying at the basal end of the left anterior wall of the common ventricle. The only other opening into this smaller cavity was the ostium of the pulmonary artery. The cavity was roughly globular in shape, with the horizontal diameter a bit longer than the vertical diameter, which measured 1.75 cm.

Beginning between the adjacent edges of the anterior and right cusps of the pulmonary valve was an irregular shelf of thickened endocardium which was ridged and divided in two. The upper part curved superiorly and was soon lost. The lower part coursed downward in a crescentic manner and spread out to form the sides and walls of a shallow pocket at the most lateral part of this cavity.

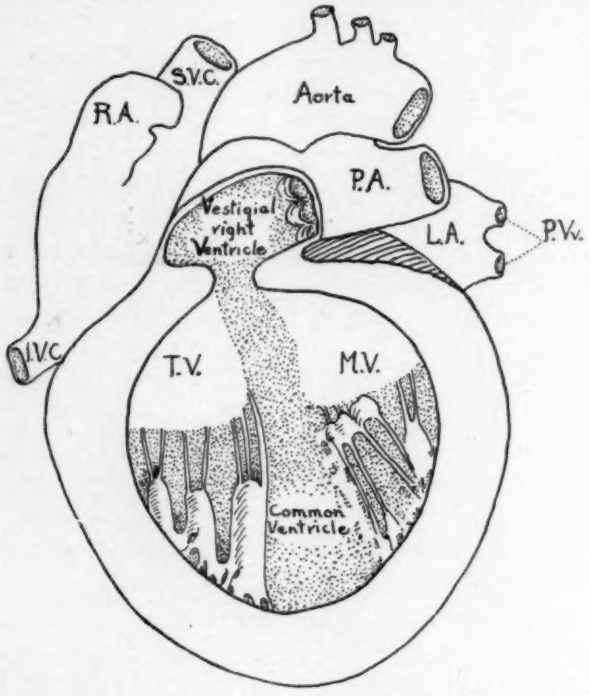

Fig. 5.—Diagrammatic sketch of the heart showing relationships of various component structures.

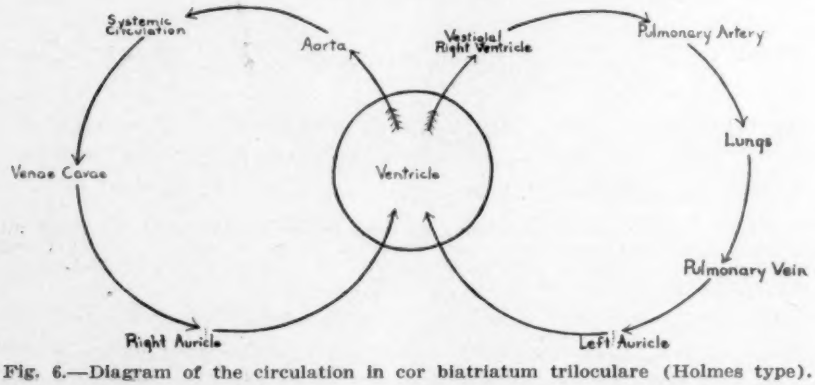

Fig. 6.—Diagram of the circulation in cor biatriatum triloculare (Holmes type).

The cavity was separated from the common ventricle beneath it by the muscular wall, which varied from 0.8 to 1 cm. in thickness. There was nothing unusual about the pulmonary semilunar cusps except that the posterior cusp displayed a hypertrophied nodulus arantii. The pulmonary artery revealed no stenosis or atresia, the diameter just beyond the valve approximating 1.5 cm. There was no communication between the pulmonary artery and the aorta.

DISCUSSION

Cor biatriatum triloculare, according to Abbott's classification,[2, 3, 4] includes all hearts which consist of two auricles and one ventricle, as well as those which have a rudimentary cavity in addition to the ventricle, in which this cavity communicates with the ventricle by means of a septal defect and with either the aorta or pulmonary artery. This latter type of heart belongs in this class functionally, although anatomically it is four-chambered.

Favorite[5] has analyzed the eleven cases which Abbott collected and was unable to find any others in the literature. He sets up the following criteria for classifying hearts as examples of functional cor biatriatum triloculare: (1) A common large ventricle, receiving the auriculoventricular orifices and the orifice of one of the great vessels; (2) defective interventricular septum; and (3) one of the great vessels leading into the rudimentary ventricle. Favorite, adding his own case, found that only seven of the eleven reported cases conformed to his criteria. Since the appearance of Favorite's report we find only one additional case, that of Kornblum,[6] which belongs in this group.

Among these nine cases of functional cor biatriatum triloculare, only one, the Holmes case, presented the untransposed pulmonary artery arising from the rudimentary ventricle. The heart which we have described is the second heart of this type.

Varying interpretations have been given regarding the pathogenesis of the anomalous interventricular septum in the Holmes heart. In Holmes' original report[1] there is apparently no explanation of the anomalous septum and rudimentary cavity. Abbott[7] believes that Holmes must have thought that the septum between these two cavities was the malposed interventricular septum, because he referred to the rudimentary cavity as the right ventricle and to the common ventricle as the left one.

Abbott[7] explains the anomaly by supposing that "at a very early period of fetal life the aortic septum had been continued downwards either to meet the septum inferius, or, that being defective, to meet the opposite ventricular wall, while the septum intermedius failed to close in and complete the division of the cavity. There would have resulted a chamber giving off the aorta and also receiving blood from both the auricles. This latter chamber, which may be considered (in Dr. Holmes' own words) the left ventricle, having thus a great excess of work to do, would have grown much more rapidly than the other. And the wall cutting off the small cavity containing the pulmonary artery would, in the subsequent growth of the heart, have been carried around to the side of the greatly enlarged ventricle and out of all relation to the septum intermedius between the mitral and tricuspid valves. And exactly the appearances seen here would have been reproduced."

Gnai[8] interprets the anomalous septum as being produced by atrophy of the cardiac bulb and hypertrophy of the left ventricle. This opinion is based on his assumption that the bulboventricular sulcus of Davis and the interventricular sulcus are the same.

Abbott's interpretation is criticized by Kornblum,[6] who states that it is difficult to understand "in view of the dynamics of the circulation, how the interventricular septum can be brought across a venous orifice in the development of the heart." Kornblum[6] assumes that the septum develops to the right of the right auriculoventricular orifice. He believes that the posterior border of the septum has grown further to the right than normal and has thus come into relationship with the right bulbar ridge on the right side of the auriculoventricular opening. Then, with further development, the bulbar ridges fusing with one another and with the interventricular septum, the right auriculoventricular ostium would remain in the left ventricle and there would be, on the right, a small chamber without a venous orifice.

SUMMARY

A clinicopathologic report of a case of functional cor biatriatum triloculare duplicating the Holmes type is presented. This is the second case on record.

We wish to thank Miss Sophie Schweich for the drawings and Dr. H. A. McCordock for the photographs.

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Society Transactions

AMERICAN HEART ASSOCIATION, 1938

The fourteenth scientific session of the American Heart Association was held June 10 and 11, 1938, at the Sir Francis Drake Hotel, San Francisco, Calif. Dr. Paul D. White, Boston, Mass., was the chairman of the program committee for the general cardiac session, and Dr. Wallace M. Yater, Washington, D. C., for the Section for the Study of the Peripheral Circulation.

The discussions of the papers presented follow.

General Cardiac Program

Discussion of the paper, "The Reversible Heart," by Dr. Rudolph Matas and Dr. Ben Heninger, New Orleans, La.

Dr. George Herrmann, Galveston, Texas.—The presentation by Dr. Matas and Dr. Heninger on the reversibility of cardiac hypertrophy in arteriovenous aneurysm cases raises several questions. Will pathologic work hypertrophy completely disappear as does the metabolic cardiac change in myxedema or the nutritional myocardial disorder of beriberi? Chemically, work hypertrophy is different from muscle mass increase of metabolic or nutritional origin. How much of the cardiac enlargement in these cases that are completely reversed is due to hypertrophy and how much is due to dilatation? At what stage does the hypertrophy become irreversible? I doubt whether great pathologic cardiac hypertrophy will ever entirely disappear as skeletal muscle atrophies from disuse.

Dr. Idys Mims Gage and I, working under the inspiration of Dr. Rudolph Matas, studied the effects of experimentally produced arteriovenous aneurysm on heart-weight/body-weight ratios. In those animals in which the A-V shunt remained open for only twelve to forty-eight hours there was no hypertrophy. In two animals in which the shunt functioned for six days and fifty-five days and roentgenograms showed cardiac enlargement, there were no increases in heart-weight/body-weight ratios. Other animals with A-V fistulas of 25, 40, 80, and 143 days' duration showed increasing grades of hypertrophy. One which had a shunt for two years and one which had a patent A-V communication for eight years showed tremendous cardiac enlargement.

It will now be necessary to determine how long an arteriovenous aneurysm may be present before it produces irreparable damage. Robbs' new technique for radiologic visualization of the cardiac chambers and for measuring the thickness of the heart walls after the intravenous introduction of diodrast may make it possible to establish and record graphically the essential facts as to the presence and the degree of hypertrophy, as well as dilatation, without sacrificing the animals. The cause of the heart changes may then be removed and the effects recorded at intervals by the same technique.

The indications in the presence of arteriovenous aneurysm, as pointed by Dr. Matas and Dr. Heninger, are for eradication of the fistulous opening or excision of the cirsoid aneurysm as soon as proper preparations can be made. The recurrence of the condition calls for repetition of the surgical treatment, as they have

demonstrated. Their cases show that what appears to be complete reversibility may be accomplished even though symptoms of cardiac failure have been present. There may come a time, however, as noted in their cases, when complete reversibility is no longer possible.

Discussion of the paper, "The Mechanism Involved in the Production of Cardiac Hypertrophy: The Effects of Digitalis on Limiting Cardiac Hypertrophy," by Dr. George R. Herrmann and Dr. George Decherd, Galveston, Texas.

Dr. Sprague.—I think this is particularly important in relation to what Dr. Herrmann said originally about the necessary courage for digitalizing patients, that is, slightly poisoning them over a long period of time. Of course, this problem of digitalizing the heart merely because it is enlarged has been quite a moot point in Boston because of Dr. Christian's espousal of that point of view some time ago. It would seem as if the evidence given here were suggestive enough to give us the courage, and the only difficulty may be that our patients will live so long that we shall not be able to study them ourselves if we digitalize them early enough.

Dr. Roy W. Scott, Cleveland, Ohio.—Although this paper presents interesting and suggestive experimental data, it seems to me that one should proceed with caution in using these observations as a basis for digitalizing patients, particularly those with hypertensive heart disease.

Certain it is that digitalis affects neither the renal vascular disease responsible for the hypertension, nor the coronary artery disease present in a high percentage of such cases. Therefore, to keep hypertensive patients without congestive failure mildly intoxicated by digitalis, in the hope of thereby limiting cardiac hypertrophy, does not seem warranted.

Discussion of the paper, "Pharmacological Studies on Cheyne-Stokes Respiration," by M. H. Nathanson, M.D., and J. P. Fitzgibbon, M.D., Los Angeles, Calif.

Dr. Howard B. Sprague, Boston, Mass.—I can confirm the findings in this paper to a certain degree because we have given somewhat over one hundred intravenous injections of this drug in the treatment of Cheyne-Stokes respiration with very satisfactory results. There is one question that I would like to ask, and that is: Have any untoward results been observed in the intravenous administration of this drug, such as transient constriction in the chest, and so forth? I am sure we would all like to hear from others who may have had experience with it.

Dr. Wilhelm Dressler, Vienna, Austria.—I may perhaps say a few words about our experience with aminophyllin, which we have been using in Vienna for more than ten years. We administer aminophyllin either intravenously or by suppositories. The intravenous injection of 7.5 grains is in general well tolerated provided that we inject very slowly and dilute the drug with 10 c.c. of glucose or saline solution.

Aminophyllin, when administered intravenously in cases of Cheyne-Stokes breathing, produces excellent results and relieves dyspnea at once, even when Cheyne-Stokes breathing does not cease entirely. It is important to know that arteriosclerotic patients suffering with Cheyne-Stokes respiration often complain only about insomnia. Frequently in such cases Cheyne-Stokes breathing is not recognized as the cause of the insomnia, since it may be indistinct during the daytime and develops fully only at night. If we are in doubt whether or not Cheyne-Stokes breathing accounts for insomnia in cases with heart conditions and left ventricular failure, it is advisable to give aminophyllin intravenously, or as a suppository at bedtime. A good effect of the drug is sufficient evidence that Cheyne-Stokes breathing was present.

Theophyllin has a similar effect when administered intravenously. We have tried caffeine, too, both orally and intravenously. Its effect on Cheyne-Stokes breathing is satisfactory, but does not last so long as the effect from aminophyllin.

We give 7.5 grains of aminophyllin intravenously once a day, and in severe cases of Cheyne-Stokes breathing even twice a day. The effect lasts for from six to eight hours. Suppositories do not work quite so satisfactorily. Sometimes the injection of aminophyllin is followed by excitement or nausea. Other unfavorable effects we have never seen.

Dr. J. Marion Read, San Francisco, Calif.—We have given aminophyllin intravenously at the San Francisco Hospital, and I can confirm what has been said about the almost immediate cessation of the cyclic breathing. There were no ill effects; but in our estimation its effect was rather short-lived. If it lasted fifteen minutes to a half hour, we considered that we were getting a fair result; that was the longest it lasted in any of the instances. We gave it, hoping we could stop this nocturnal cyclic breathing which is so disturbing; but we discontinued it because we found the effect was not sufficiently long-lived to warrant its continuance.

Dr. Nathanson (closing).—We did see a few reactions, but none were serious. In several instances, the injection was followed quite promptly by flushing of the face, sweating, nausea, and increase in heart rate. I did not cover in our report some observations on therapy directed at the prevention of nocturnal dyspnea and restlessness, such as were mentioned by Dr. Dressler. A typical case that I have in mind is that of a patient with hypertension who is comfortable during the day, shows no evidence of pulmonary congestion, and has a vital capacity of 4000 c.c., which is practically normal for this patient. Yet periodically this patient is disturbed at night by marked restlessness with respiratory distress. In this case and in several of a similar type, theophyllin in special enteric tablets was administered late in the day in large doses. The amount used was usually 0.6 gm. to 0.8 gm. in divided doses. The results obtained indicate that there is a place for the oral use of theophyllin compounds in the prevention of nocturnal restlessness and respiratory distress.

Discussion of the paper, "Hypertensive Heart Disease: A Clinical and Pathological Study of 369 Fatal Cases," by Dr. Francis D. Murphy, Milwaukee, Wis.

Dr. D. J. Glomset, Des Moines, Iowa.—I have been very much interested in the paper just presented by Dr. Murphy because recently I have examined rather minutely the coronary arteries of about one hundred hearts for the purpose of determining the degree of arteriosclerosis present. There were over thirty hearts from patients with hypertension in this series. Approximately one-half of them showed only slight arteriosclerosis. The arteries of all were very large. Hence it is logical that the capillaries should also be large. A search for arteriolosclerosis was also made, but none was found.

Discussion of the paper, "The Application of Tomography in the Demonstration of the Pulmonary Anatomy," by Dr. Alexander Petrilli, San Francisco, Calif.

Dr. William J. Kerr, San Francisco, Calif.—Dr. Petrilli's contribution is a very important one. I can see great possibilities in anatomic study by comparing his films with frontal sections made after death, along the lines followed a good many years ago by Norris and Landis, of Philadelphia. Certainly we shall be able to clarify a good many of the pulmonary findings in patients with enlarged auricles compressing the arterial branches; details of the vessels would be more readily seen; and we should be helped in other conditions, such as aneurysms of the pulmonary artery, obstructions of arteries by tumors, and a great many other conditions.

I think it is a very interesting approach to this study.

Dr. Petrilli (closing).—There are different ways of obtaining these sections, as you probably all know; this is the method known as tomography, in which the tube moves in one direction only; there are other variations of this apparatus which give essentially the same results. There will undoubtedly be a long period of discussion lasting over many years as to which method is the best, but eventually we shall use the one that we like.

Discussion of the paper, "Calcareous Disease of the Aortic Valve," by Dr. Frederick Willius and Dr. Thomas J. Dry, Rochester, Minn.

Dr. William Stroud, Philadelphia, Pa.—In the cases of this disease that we have had in Philadelphia, we have been very much impressed with the excellent prognosis. I am sure, as Dr. Willius has said, that we are going to be more and more surprised as we look for these calcareous changes in the roentgenograms.

Dr. Louis Faugeres Bishop, Jr., New York, N. Y.—In studying the bicuspid aortic valve, following the method described by Lewis and Grant, we found it possible to differentiate a congenital raphe or a fused commissure ridge in aortic valves which were the seat of advanced calcification and stenosis.

I wanted to ask Dr. Willius whether he has encountered congenitally bicuspid aortic valves in any of his examples of calcareous disease.

Dr. Willius (closing).—We did not encounter any case of bicuspid aortic valve in this series. There was one very interesting case, however, which I would like to mention. Complete fusion and calcification of the three cusps had occurred, resulting in complete obstruction of the orifice, and through a fortuitous circumstance a small fenestration in one cusp occurred, which was the only communication between the left ventricle and the aorta.

Discussion of the paper, "Dehydration Through Glycosuria: Experiments With Phlorhizin as a Diuretic," by Dr. Wilhelm Dressler, Vienna, Austria.

Dr. Charles N. Hensel, St. Paul, Minn.—I have been much interested in listening to Dr. Dressler's report on the use of phlorhizin as a diuretic because I have at the present time a patient with an intractable edema who might benefit from the use of this remedy. She is an elderly diabetic who came in with acute congestive heart failure and hydrothorax requiring thoracenteses. She was placed on a regular diet and insulin but continued to be troubled by dropsical accumulation. For a long time salyrgan was successful in bringing about diuresis. When the veins became sclerosed, mercupurin was substituted. Within the past few months albumin and casts are appearing in the urine in increasing amounts, evidently due to the mercury radical in the mercupurin.

It seems to me that phlorhizin might be distinctly beneficial in this particular patient, provided it does not produce liver damage. As I recall, Dr. Dressler stated that the diuretic action of phlorhizin arose through preventing the resorption of sugar in the urinary tubules. If this is so, may we not have to watch the level of blood sugar, which may be reduced to a point of hypoglycemia as a result of the action of phlorhizin?

Dr. Wilhelm Dressler (closing).—As to diabetes, it has been advised to give phlorhizin in order to lower the blood sugar level. I have used phlorhizin as a diuretic in one diabetic case, and it produced an excellent diuresis.

German and American authors have repeatedly emphasized that phlorhizin is harmless in the doses ordinarily used. Nevertheless, we ought to be very careful until we have gained more complete experience, both from animal experiments and from treatment of patients, to be sure to avoid any injury to the patients.

In the case of ascites mentioned above, I would try to administer mercupurin intraperitoneally; this therapy sometimes gives excellent diuretic results.

Discussion of the paper, "Incidence of Coronary Disease in Cases Autopsied at the Massachusetts General Hospital," by Dr. W. H. Gordon, Dr. Edward F. Bland and Dr. Paul D. White, Boston, Mass.

Dr. Howard B. Sprague, Boston, Mass.—This paper can be considered an early step in the attempt to determine some of the factors which are responsible for arterial change from a point of view of economics and of some of the wider aspects of the problem.

I just want to mention that if any of you in your travels throughout the world have any opportunity to study social conditions in which a people is set up definitely into layers, it may contribute considerably to progress in this analysis. I mention this particularly in relation to an observation that Dr. White made on his recent trip to Mexico, where he felt that the people were divided very clearly into two completely separated economic and social groups with respect to the manner of living and nutrition, so that there are opportunities to study this subject in man under conditions which rather closely approximate animal experiments.

Discussion of the paper, "The Prognosis of Bundle Branch Block," by Dr. Louis Faugeres Bishop, Jr., New York.

Dr. William J. Kerr, San Francisco, Calif.—It probably would be of interest if Dr. Bishop would say something about the life expectancy in this group of patients who survived.

Also I would like to ask him a question, that is, whether syphilis played a very considerable role as the cause of death in the younger age group of those who suffered from this condition.

Dr. John J. Sampson, San Francisco, Calif.—The prognosis for patients with bundle branch block that Dr. Bishop gives confirms the opinion which was given by Miss Nagel and myself, based on three hundred cases that were studied at the University of California Hospital about three years ago. The fact which he demonstrates, in agreement with our data, is that the individuals destined to die do so fairly soon after the discovery of the lesion; such seriously ill patients increase the fatality rate of the entire series.

In our particular series the number of patients who died rose very rapidly within the period of the first year. Between the first and third years, the curve of mortality was definitely less steep, and after the fifth year the curve flattened out very much as Dr. Bishop's curve did.

We likewise reported one case of seventeen years' duration. There were a few other interesting observations in our series which were not noted by Dr. Bishop, namely, that it is extremely rare to find bundle branch block in cases of congenital heart disease and that the commonest occurrence of bundle branch block was in coronary arteriosclerosis.

I would like to hear Dr. Bishop's statement as to his estimate of possible life expectancy in patients with this lesion. We determined our life expectancy in our series of cases and found that if these individuals lived over one year after the discovery of the bundle branch block their chances of a normal life expectancy increased approximately 50 per cent, and again increased approximately 25 per cent within the next two years. If a patient had survived approximately five years after the time of the discovery of his bundle branch lesion, we found that the bundle branch block alone would have practically no influence on his life expectancy.

Dr. Oscar F. Johnson, Sacramento, Calif.—In the first place I want to compliment Dr. Bishop on his excellent paper. We ordinarily think of bundle branch lesion as due to arteriosclerosis or syphilis. At this time I should like to state that I have a 43-year-old patient under observation who has a bundle branch lesion. When

I first saw him, he was referred to me because of tingling and numbness in his fingers. He often awakened at night with a choking sensation. He was examined very carefully, but there was no demonstrable cause for his bundle branch lesion. He stated that about eleven or twelve years ago he was in an automobile accident. He sustained a terrific steering-wheel blow across his chest. He was unconscious for a few hours. Recovery was uneventful. I mention this case because I think the cause of the bundle branch lesion was trauma. During the past year the patient has enjoyed excellent health except for moderate shortness of breath.

Dr. Howard B. Sprague, Boston, Mass.—I think I will have to say something in an attempt to explain some of the rather crude figures of an earlier day.

Dr. Bishop reported cases, about nine hundred in number, and a third of those are the ones reported by Graybiel and myself some years ago with a mortality much higher than he reports.

It seems perfectly clear, I think, and we would all agree with his conclusions, that it is the underlying degree of cardiac disease which is the important factor in the prognosis. We have come to believe that bundle branch block, when it is merely a part of the whole coronary involvement, does not really add so much to the gravity of the prognosis.

But there are constantly appearing instances in which bundle branch block apparently is the result of a very localized coronary occlusion of smaller vessels which supply the conduction system alone, and therefore does not indicate such a poor prognosis. After all, is not this another example of what happens when one takes electrocardiograms on a lot of people suspected of cardiac disease, instead of a lot of people who have obvious cardiac disease, as was done in earlier series?

Undoubtedly, we shall find many patients with bundle branch block who will live for a long time. It is very much like coronary thrombosis in general.

Not so many years ago, we had the idea that everybody who had coronary occlusion died. Now, by taking electrocardiograms on everybody who has a pain in his stomach, we find "coronary" T-wave changes, and we know a great many people recover and live for years.

Bundle branch block is not a pleasant thing to find in anyone, just the same; 58 per cent of Dr. Bishop's patients are dead, and I would not advise the insurance companies even now to consider this a very good risk group.

Dr. Bishop, Jr. (closing).—I want to thank the discussants for their very interesting discussion.

First, I want to apologize to Dr. Sampson for not including his cases. He has arrived at the same conclusion, that, if these patients survive a few years with bundle branch block, their chances seem to be greatly increased.

With regard to the question of syphilis, only two patients in our series had syphilis. These were observations from private practice where cardiovascular syphilis is relatively rare.

I can only agree with Dr. Sprague entirely in what he says that as the result of the development of cardiology we are now taking a great many more electrocardiograms, and our viewpoint is changing about prognosis in general. I believe that the underlying heart disease is the important point.

Discussion of the paper, "The Relationship of the Early Treatment of Syphilis to the Later Development of Evidence of Cardiovascular Syphilis," by Dr. W. P. Thompson, Los Angeles; Dr. W. J. Comeau and Dr. Paul D. White, Boston, with the assistance of Dr. J. McMillan, Dr. B. Wise, Dr. W. C. Reed and Dr. W. H. Gordon.

Dr. J. C. Carr, Chicago, Ill.—I am particularly interested in this paper because the authors have discussed a subject to which we gave much attention several years ago at the Cook County Hospital.

We studied the autopsy reports for two years with the cooperation of Dr. Jaffe and found that in this period syphilitic aortitis was noted 229 times. Aortic regurgitation was responsible for the death of about 13.5 per cent of this group, and autopsy revealed the presence of well-developed aortic regurgitation in 16 other cases, a total of 49, or 21.6 per cent. In 53 instances, or 23.2 per cent, aortic regurgitation or aneurysm was responsible for death.

Now, the interesting thing to us was this: In this large group, no single patient had reported adequate treatment. One patient, a woman with syphilis of the nervous system, reported that she had had twenty-eight "shots." This woman and another woman with neurosyphilis had some treatment for late disease, but no early treatment whatever. My recollection is that there were only nine patients in this entire group who reported that they had ever had treatment.

To us it appeared that the result of this study warranted one statement, viz., that the late results of syphilitic aortitis, the types of cardiovascular disease which are responsible for the death or for the incapacitation of these patients over some years, are wholly preventable. That is the reason I want to emphasize what the authors concluded from a different approach.

Our statistics were based upon the records of the Cook County Hospital. So far as private practice is concerned, we see cardiovascular syphilis only occasionally. It seems to me that the one important lesson we need to bear in mind wherever we are working is that patients with neglected syphilis stand a very good chance of dying, within some twenty years after the initial infection, of some form of cardiovascular syphilis.

So far as these statistics were concerned, 26 per cent did die of syphilitic aortitis and its complications on an average of 22 or 23 years after the initial infection, and in another 14 per cent anatomic evidence of well-developed complications of syphilitic aortitis was discovered at autopsy.

Section for the Study of the Peripheral Circulation

Discussion of paper, "Tissue Pressure: An Objective Method of Following Skin Changes in Scleroderma," by Dr. William A. Sodeman and Dr. George E. Burch, New Orleans, La.

Dr. Winchell McK. Craig, Rochester, Minn.—One of the great difficulties in attempting any therapeutic measure for chronic conditions such as this is the evaluation of results. And I think one of our great difficulties in attempting to treat scleroderma has been the fact that we had no method, or measuring stick, by which to judge our results.

This ingenious method certainly opens up possibilities and allows us to evaluate the results following operation in a quantitative way and, as has been depicted on the screen, we do not have to wait to evaluate it by observation.

I am tremendously interested in this and think it has a very important place in the treatment of scleroderma.

Dr. A. W. Duryee, New York, N. Y.—A year ago before this Section we reported from the Post Graduate Hospital thirty-four cases of scleroderma, in twenty-seven of which the patients had been treated by mecholyl, and at that time the only means of demonstrating improvement was increased motion and flexibility of the skin.

Following some suggestions at that meeting, we have attempted during the past year to measure tissue pressures and skin conductivity. At this time we are not prepared to give a final report, but the thing that strikes me in all of the work we have done so far is that with improvement in certain areas sclerodermous patches develop in other areas, so that in order to check up carefully on any individual many

readings must be made over the various parts of the body, and although you may record a drop in tissue pressure in any one place, it may mean a marked increase in another location.

I think we have from this paper some very interesting data that we can use in further checking results.

Dr. Sodeman.—This method and the determination of tissue pressure throw light as well upon the mechanism of the vascular changes in scleroderma. The changes are supposedly of two types: one, a primary change, with secondary scleroderma, and the other, a secondary vascular change.

You can see from the figures thrown on the screen that some of these values are higher than the normal capillary pressure. Thus in order for the circulation to be adequate, pressure would have to build up from the arterial side and increase the capillary pressure and the venous pressure in order to complete the circulation through that part. Apparently, therefore, the elevations in tissue pressure are important in the vascular changes which occur secondary to the sclerodermous process. It is difficult to insert needles into veins in the dorsum of the hand in a patient with a thick skin. We have accidentally punctured veins in sclerodermous areas and made determinations of venous pressure upon those individuals, for this apparatus can determine venous pressure as well. We found that the venous pressure was elevated in those areas in which the tissue pressure was markedly elevated, whereas a determination of the venous pressure closer to the heart showed that the venous pressure was in the normal range in areas in which the scleroderma did not occur.

Dr. I. H. Page, Indianapolis, Ind.—I would like to ask Dr. Burch how constant these readings are, that is, over a period of time, in the same place. Are the figures in the first column the average of all the results of one reading? If so, how constant are those readings from day to day?

Dr. Burch (closing).—In all our determinations we make three readings. These readings have always agreed within ±1 mm. of water. In normal individuals we have made determinations from day to day in the same area and found variations no greater than 4 mm. of water.

In making repeated determinations we should be careful to use exactly the same area. As has been mentioned, there are variations from area to area, and, since scleroderma is a rather patchy disease, if we do not use the same area we are likely to obtain results which will not agree. And, of course, the more determinations we make in different areas the more valuable the information.

Discussion of the paper, "Bilateral Carotid Sinus Denervation in a Patient Having Syncopal Attacks and Congenital Vascular Anomaly," by Dr. Albert H. Elliot, Dr. Neville T. Ussher, and Dr. Caleb S. Stone, Santa Barbara, Calif.

Dr. Morris H. Nathanson, Los Angeles, Calif.—The report presented by Dr. Elliot and his associates describes a rather unusual type of syncope associated with a sensitive carotid sinus.

There is no question that a sensitive carotid sinus may be the basis for attacks of syncope. In an individual suffering from dizziness or syncope in whom the characteristic symptoms may be reproduced by carotid pressure, there is little doubt that the diagnosis is carotid sinus syncope. However, there are many individuals, especially elderly men, in whom carotid sinus pressure produces prolonged cardiac standstill and syncope, who never develop spontaneous attacks due to cerebral ischemia. In fact, in a routine study of the carotid sinus reaction, I found about 60 instances of extremely sensitive carotid sinus reactions on repeated testing. On

questioning these individuals, it was found that dizziness or syncope occurred in less than 10 per cent. It is, therefore, possible that syncopal attacks and a sensitive carotid sinus may be present in an individual with no etiologic relationship between the two.

I have studied for the past four years the action of drugs on the cardiac standstill which can be induced in many individuals by pressure on the carotid sinus. The only substances which are effective are adrenalin and chemically related compounds, the sympathomimetic amines. Recently, I have studied a new compound of this group, paredrine (parahydroxyphenylisopropylamine); this compound is stable, effective on oral administration, and about two to three times as active as ephedrine. Paredrine also has an advantage in that it does not produce the unpleasant side effects of ephedrine. I have treated several patients suffering from syncopal attacks associated with a sensitive carotid sinus with this drug and have had favorable results.

I have, up to recently, not observed any harmful effects from the testing for the response to carotid sinus pressure and have carried out this test on several hundred individuals. Recently, however, a patient entered the hospital with a history of syncopal attacks. The resident, suspecting a sensitive carotid sinus, very properly tested the patient by pressure over the carotid sinus. A cardiac standstill of several seconds followed, associated with jerky movements of the right arm and leg with the development of a right hemiplegia.

Discussion of the paper, "Factors Influencing Blood Pressure Determinations: Accommodation to Postural Change and Transient Differences in the Two Arms," by Dr. Eric Ogden and Dr. Nathan W. Shock, Berkeley, Calif.

Dr. W. D. Stroud, Philadelphia, Pa.—For the past eight years, I have been taking the blood pressure in both arms of all patients that have come to me, and I can confirm the impression that has been given by this last paper, namely, that there is quite a marked difference in the blood pressure in the two arms in a vast majority of cases.

Of course in an office examination one cannot control all the factors involved as well as they have been controlled in this presentation.

The main reason I have taken the blood pressure in both arms is that eight years ago, before the insurance companies had stopped granting total disability insurance, one of Walter Camp's "all-American" football players took out life insurance containing a total disability clause. His blood pressure was taken by the insurance doctors in the left arm only. His was a $250,000 policy taken up by three or four companies. This individual had a blood pressure of 120/80 in the left arm. Three weeks after he took out this policy, a cardiac infarct developed while he was playing golf. I saw him six weeks after this infarct occurred, and at that time he had a blood pressure of 120/80 in the left arm, but a pressure of 200/110 in the right arm. Presumably then, if these companies had taken the blood pressure in both arms, this gentleman would not have been living in Santa Barbara for the last eight years on his income from this total disability insurance!

Also, I think it is a very good procedure since nowadays all the general practitioners have electrocardiographs and know as much about cardiovascular disease as we do, and yet few of them take the blood pressures in both arms. If we, as cardiologists, when seeing patients in consultation, take the blood pressure in both arms, then, at least, we have done *one* thing the average general practitioner does not do!

Discussion of the paper, "The Precision of Individual Blood Pressure Measurements," by Nathan W. Shock, Ph.D., and Dr. Eric Ogden, San Francisco, Calif.

Dr. Ogden.—I do not think there is much to be added to this, except to repeat the warning that Dr. Shock gave. We have been making studies in which we hope to use pulse pressure measurements for computation of metabolic rates, according to Dr. Read's formula, and for other purposes, and therefore it was important to see how precisely they could be made.

This indicates the best that we can do. It is not an indication of precision which any of those three observers can expect to get in a casual, clinical measurement. It represents the best that they can do, and I certainly hope there will be no misinterpretation of that. None of us feels that there is a possibility that in the ordinary way our systolic pressure measurements are good to 1.5 mm. of mercury, because they certainly are not.

Another thing is this: the last curve that Dr. Shock displayed shows very effectively the necessity of making three or four readings and the comparative increase in worth of making ten or a dozen readings to assess a particular blood pressure.

Everybody in this group has found by experience, doubtless, that a single reading is useless and that three or four readings are valuable. One value of determining this quantitatively is, I think a matter of teaching, inasmuch as the young man who is just learning to take blood pressures is inclined to be less skeptical of proof like this than of a statement of clinical experience. If somebody says, "I find that it is necessary to take three or four readings," he is likely to doubt it and to want to learn it himself. If you can show him by a statistical presentation why it was necessary to take three or four readings, he is going to save quite a good deal of time which he would spend in learning over for himself the things which have already been learned by other people.

Discussion of the paper, "Factors of Error in Blood Pressure Readings," by Dr. Irving S. Wright, Dr. Ralph F. Schneider, and Dr. Harry E. Ungerleider, New York, N. Y.

Dr. Eugene S. Kilgore, San Francisco, Calif.—I am so amazed by this paper that I hardly know where to begin the discussion. To explain, it will be necessary to go back a number of years and describe certain personal experiences. I had undertaken a research among college students which required many blood pressure measurements under varying conditions. Desiring an impeccable technique, I consulted the physiologic and the clinical books and found them united in regarding the Erlanger instrument as the most accurate. It furnishes graphic oscillatory indices for systolic and diastolic points, and the readings are made from a mercury column at the moment when these oscillatory phenomena appear on the smoked drum. In my work this necessity for hasty judgment was eliminated by including on the graphic record a curve showing the changing mercury manometer level simultaneously with the pressure oscillations. Since I fancied the personal factor of error was thus entirely eliminated, I was later much annoyed to find that I could not honestly decide just where the systolic and diastolic criteria appeared on most of the oscillation graphs. Study only increased the confusion; but at length, overcoming my feeling of inferiority, I changed the direction of the research, making it a study of the personal factor of error in the oscillatory blood pressure method—not among novices but among well-known professors of medicine and of physiology. A half dozen of them, including Professor Erlanger himself, served as subjects of the experiment. Each received a photographic copy of the same one hundred oscillation graphs selected at random, and returned the copy after

marking systolic and diastolic reading points. These individual reading points were then assembled on a fresh copy and were expressed in millimeters of mercury. There were discrepancies aplenty. In fact the reading points of different observers were scattered all over the graphs, and in some cases the diastolic reading of one man was actually higher than the systolic reading of another. In continuing the experiments it was shown that one individual (a chief exponent of the oscillatory method) could not mark a second copy of the same one hundred graphs without considerable deviation from his first marks. And the conclusion was inescapable that the oscillatory method was enjoying a most unmerited reputation for reliability.

With several associates I then studied the personal factor of error in the use of the palpatory and the auscultatory criteria. It was found to be comparatively small in both of these methods. And, contrary to another general assumption, it was found that for systolic readings the personal error factor was substantially the same for the auscultatory method as for the original and simple palpatory method. To be sure, the auscultatory readings average a little higher than the palpatory, but that is of no practical consequence. Consistency is all-important; and it was apparent that the net result of a great deal of work and writing had been to introduce and popularize techniques which did not improve consistency of readings, but in some cases had a very contrary effect.

Well, all this was sent on and published in the *Archives of Internal Medicine* in 1915. Just the facts. It seemed superfluous to state the obvious inferences: that the oscillatory method should be given up altogether and that for systolic readings the simple, convenient and nearly fool-proof palpatory method should be readopted as standard for ordinary clinical use and for insurance examinations. For it had already been pointed out that the arterial sounds are not infrequently deficient or absent in the vicinity of systolic pressure—the so-called "auscultatory gap." And the fact is that gross errors in reading systolic pressure by the auscultatory technique are not uncommon.

Our findings have never been controverted. But were these inferences reflected in general practice? Not at all. On the contrary a new graphic oscillatory machine appeared on the market, without pretending to obviate the errors we had found so great in the oscillatory technique; and, favored with an efficient sales force and the always potent appeal of a very high price, it enjoyed wide acceptance. And those who cannot afford or cannot conveniently carry about the oscillatory machine almost invariably continue to rely on the arterial sounds for systolic readings. Some maintain that auscultatory systolic readings should be "controlled" by the finger on the radial artery, but in practice this is rarely done.

These authors have performed the very important service of focusing attention upon an important and much neglected topic. The data assembled show shocking lack of agreement on blood pressure technique among teachers of medicine. But to me the amazing fact is the continued neglect of the palpatory method for systolic readings. The authors of this paper have repeated experiments similar to mine for the auscultatory method and have found the personal error factor about what I found it—an appreciable but clinically not very important error in the general run of cases. But they have not reckoned with the occasional very large error of the auscultatory method for systolic readings, and they have not even considered the use of the palpatory method in which the personal error factor compares favorably with that of the auscultatory method and in which the occasional very large error does not occur. And finally, the most amazing of all is the neglect of insurance companies to insist on the palpatory method for systolic readings, for this is a neglect which costs them money.

Dr. Carl J. Wiggers, Cleveland, Ohio.—There are several compelling reasons why I ought to make a few comments:

1. I am responsible for initiating the instruction in methods for determining human blood pressure at Western Reserve University Medical School. This is a function of a physiology department. No student is promoted to clinical years without a practical test as to his ability to measure blood pressure in accordance with several criteria. In addition, they profit from experience in clinical years, so that instruction is not at fault.

2. I also have had various experiences that can be added to those enumerated today which indicate confusion as to methods for determining blood pressure. In examining National Board candidates, I am usually surprised to find how my blood pressure fluctuates. Again, in three successive examinations for life insurance my systolic pressure was read as 120, 140 and 180 mm. Hg by three examiners for different companies. The last reading was obviously a technical error, and I could not resist the suggestion that if the cuff were applied on the inside of the arm rather than the outside, it would be easier to compress the artery against the bone than to bend the bone toward the artery. This illustrates that careless technique rather than the criteria may be at fault.

3. Few physicians (or investigators) keep in mind the limitations set by the criteria utilized to estimate systolic and diastolic pressures. As tested by hypodermic and optical manometers, systolic and diastolic pressures in the large arteries vary from beat to beat. With normal respiration and rhythmic heart action the variations easily reach 10 mm., while during dyspnea and marked cardiac irregularity the differences are so extreme that no single figure has any significance. Since even normal blood pressure varies in this way, refinements of technique or statistical analyses which claim to measure pressures with an accuracy greater than 5 (or 10?) mm. Hg merely result in delusions of a degree of accuracy which does not exist. However, clinical measurements are still useful even if errors of 10 mm. are incurred.

4. I have checked, over a period of years, a large number of different criteria and also various instruments purporting to make readings more exact. I still feel that the auscultatory method is *generally* the best. We teach that the first sound heard on decompression signals the *highest* systolic, and the appearance of all sounds, the *lowest* systolic pressure during respiration or arrhythmic cycle. However, as Dr. Kilgore suggests, these should always be checked by the palpatory method, for instances occur clinically in which the readings by the latter method may be higher. The auscultatory method is not applicable under certain conditions. Similarly, determinations of diastolic pressure by use of the 4th phase of "decompression sounds" should always be checked by complete disappearance of sounds, and if these do not agree within 5 or 10 mm. the diastolic pressure reading is doubtless faulty. For example, notations of diastolic pressure readings of 15 or 0 mm. in aortic insufficiency are absurd; they are dynamically impossible.

5. Finally, I question whether improvement in the utilization of criteria and employment of apparatus is likely to be achieved through rules promulgated by committees or assemblies. Different criteria must continue to be used under different conditions. We ought rather to seek means for awakening the conscience of physicians to the need of exercising every care. State legislatures or Congress might even pass laws defining the procedures that physicians must follow; but such laws would not make our pressure readings any more exact. Physicians will always insist on freedom to use methods which they individually believe to be the best.

Dr. W. J. Kerr.—I do not know how much Dr. Wiggers' conscience is bothering him this morning, but if it is not troubling him, it probably will be. If the American Heart Association appoints a committee to study the standards for making blood pressure estimations, we certainly hope that men like Dr. Wiggers, Dr. Erlanger, and Dr. Kilgore, who may be protagonists on certain points of view, would be on that committee.

I am certain we do not want to bend any bones in order to get the readings of blood pressure, but we hope to have a committee who will study this and, if necessary, set up some standards that we may be able to follow.

I am sure if Dr. Wiggers' students are like ours, when they get out they have about as many different methods as there are students.

Dr. Ungerleider (closing).—I want to thank the various discussers, and especially Dr. Kerr for coming to my rescue.

If I did not mention anything about the palpatory method as far as the medical schools are concerned, it is because the medical schools themselves did not mention it in their questionnaires. The three replies which did mention the palpatory method of taking blood pressure were those from three insurance companies.

Further, our paper was simply an exposition of the methods taught and used. We did not start out to say which method was the best to use. Being a life insurance medical director, I am at a disadvantage here, of course, but nevertheless, I do feel that we ought to have some standard method of measuring blood pressure.

We do find that mortalities vary with various small increases in blood pressure. Life insurance companies have just concluded a mortality study of over 900,000 people, and it is a rather interesting fact that with every 5 mm. of increase over the average blood pressure the mortality has increased, so much so that, when you leave the accepted clinical limit (I am saying that with a question mark) of about 145 millimeters of mercury, mortality increases by large amounts.

We in life insurance feel that there should be some method by means of which all concerned will talk the same language, that if a reading is designated a systolic reading, we have some idea of where it was read, and if it is diastolic, where that was read.

I feel that Dr. Wiggers is probably correct when he said that we should not be regimented by any committee, but I do, nevertheless, believe that some start should be made.

Discussion of the paper, "The Sulphocyanates in Hypertension," by Dr. M. Herbert Barker, Chicago, Ill.

Dr. Winchell McK. Craig, Rochester, Minn.—I should like to ask Dr. Barker about his experience with the administration of sulphocyanates after splanchnic resection in order to round out his very interesting observations. These post-operative studies are important as they may play a part in the ultimate treatment of hypertension.

Dr. Louis Faugeres Bishop, Jr., New York, N. Y.—I should like to ask if there have been any electrocardiographic observations during the course of this study which would lead us to believe that the cyanate therapy has a direct effect on the myocardium.

Discussion of the paper, "A Practical Method of Visualization of the Chambers of the Heart, the Pulmonary Artery, and the Great Blood Vessels in Man and Its Clinical Application," by Dr. George P. Robb, and Dr. Israel Steinberg, New York, N. Y.

Dr. Howard B. Sprague, Boston, Mass.—Certainly there is no question about the great potential value of this type of study because one immediately realizes in one's own experience, I am sure, cases in which such information would be of great value. We have had such problems, particularly of syphilitic involvement of the great vessels and congenital abnormalities, in which this particular technique would have helped a great deal. It is a technique which is apparently safe, and that is the first thing we have to think about; and it has been tested on patients who have been severely ill.

I would like to congratulate the originator of this method and trust that many of our clinics will now go ahead and experiment with it.

Dr. William J. Kerr, San Francisco, Calif.—Mr. Chairman, I must apologize to you all and to the speaker. Because of the many details arising in connection with the meeting in our city, it was impossible to get back in time to hear this paper presented.

I have heard a good deal about this work, however, and have been tremendously interested in the possibilities the method offers for further study of the chambers of the heart and the dynamics of the circulation. I am sure it is going to be a very valuable method if it is safe to employ it in the study of a good many types of clinical conditions.

I regret that I cannot say more about it at this time.

Dr. Robb (closing).—As to the question of dosage, it varies roughly with the body weight. In normal persons 35 c.c. of the 70 per cent solution of diodrast is usually enough for visualization of the heart and the aorta. For pulmonary arteriography, 30 c.c. usually suffices because a lower concentration gives sufficient contrast in the lungs.

However, in patients who have thick chests, enlargement of the heart or aorta, or pulmonary enlargement, it has been necessary to increase the amount. The maximal dose has been 45 c.c.

Question from the floor.—At what rate?

Dr. Robb.—The injection should be completed in two seconds or less. Such rapidity is contrary to accepted clinical practice and was adapted only after cautious trial had proved that it was safe. Determinations of the arterial and venous blood pressure, and electrocardiograms and clinical observations made continuously during the injection and repeated afterward, have revealed no adverse effect upon the heart.

The rapid delivery of the diodrast into the superior vena cava is achieved by the forcible flushing of the peripheral vein with blood after the injection. The blood is withdrawn into the syringe before injection and, being lighter, rises to form a column above the diodrast.

Question from the floor.—What is the size of the needle you use?

Dr. Robb.—A 12 or 13 gauge needle one and one-half inches long is used in adults. It is advisable to test its location within the vein by the injection of normal saline solution. This is readily done since the needle is attached to a two-way stopcock before insertion into the vein.

Discussion of the paper, "Analysis of Results Following Sympathectomy for Peripheral Vascular Disease," by Dr. Géza de Takats, Chicago, Ill.

Dr. Frederick Leet Reichert, San Francisco, Calif.—I am indeed sorry that Dr. de Takats was not able to attend the meeting, but I have enjoyed giving his paper

and agree with him that interruption of the sympathetics to the extremities is of definite help in the treatment of peripheral circulatory disturbances.

Out here most of these patients are seen in the Outpatient Clinic of Stanford University Medical School, and, as the economic recession has been of such long standing, we have not been able to have them enter the hospital for operative removal of the sympathetics. In many instances we have resorted to interruption of the sympathetics with alcohol injections.

We prefer the operative removal of sympathetics for the upper extremity and, in many instances, the alcohol injection for the lower extremity.

Dr. de Takats has mentioned the importance of classification of the cases in determining the degree of structural involvement as a criterion for operation on the sympathetics and whether it will be successful.

Several years ago we performed a number of tests on these patients, but we soon learned that environmental temperature was important and that we could not tell whether there would be a good result unless the patient was in a cold environment. Since putting them in a cold environment is harmful, we have dispensed with many of the elaborate tests and depend upon the circulatory appearance of the extremity and the history in deciding what is to be done. In reality, it does not make very much difference to us now whether we classify the cases as Raynaud's disease, Buerger's disease, or arteriosclerosis, as our treatment is much the same.

We force fluids, have the patients stop tobacco, and teach them the importance of being in a warm environment. When they have learned these things, we may try venous hyperemia or passive vascular exercise, or we might suggest interruption of the sympathetic chain. The patient is told that by sympathetic interruption we are attempting to give him vasodilatation twenty-four hours of the day, and also that we are simply treating a symptom so that he must regulate his life accordingly.

I do feel with Dr. de Takats that we do not see the early phases of these conditions and perhaps if we make our patients realize the importance of the proper care of their legs, which have been carrying them around for many years, and if we, as physicians, realize that in patients over forty years of age it is more important to feel for the pulses in their feet rather than the radial pulse, we may be able to help these individuals a great deal without any surgical treatment.

Our results have been good in what Dr. de Takats calls reflex dystrophia and causalgia in painful amputation stumps, as well as the cold, spastic extremities that occasionally follow hemiplegias.

Dr. Winchell McK. Craig, Rochester, Minn.—I think Dr. Reichert has covered the subject very well. Also, he has brought out one matter that I think is important; namely, that the economic situation of the patient determines the method of treatment. I am very much interested in the results which he has been able to obtain in the outpatient department.

Discussion of the paper, "Skin Temperature Studies After Sympathectomy and Deafferentation," by Dr. Robert A. Phillips, Dr. James D. Hardy, and Dr. Joseph C. Hinsey, New York, N. Y.

Dr. Edgar V. Allen, Rochester, Minn.—A few months ago, when I was in New York, I had the opportunity of visiting Dr. Phillips' laboratory and discussing some of these problems with him.

The point which he makes, in brief, is that he has a method which he has worked out with Dr. Hardy and Dr. Hinsey whereby he may determine how much blood is shunted from a part, at least from the skin of that part, as a result of any procedure such as the intravenous injection of adrenalin.

You may know that sympathectomy for Raynaud's disease of the lower extremities results in cure in almost all instances. The results of the operation in cases

of Raynaud's disease of the upper extremities are much less satisfactory. When the neurosurgeon performs lumbar sympathectomy, he cuts the preganglionic fibers, because the ganglia which supply the lower extremities are distal to the lumbar ganglia, but when performing sympathectomy for Raynaud's disease of the hands he removes the ganglia which supply the upper extremities.

This led to an ingenious explanation for the difference of results in operations for Raynaud's disease of the upper extremities, namely, that the operation for the lower extremities, which was preganglionic, did not produce greatly increased sensitivity to adrenalin as did operation for the upper extremities, which was postganglionic.

The recurrence of color changes after cervicothoracic sympathectomy was supposedly due to increased sensitivity of arterioles to adrenalin. That gave us all very much hope that the same type of operation could be performed for Raynaud's disease of the upper extremities as was performed for the lower extremities, namely, preganglionic section, and such an operation was devised.

Unfortunately, that operation did not produce as good results as anticipated, and certainly not as good as those which follow lumbar sympathectomy for Raynaud's disease. Thus, the explanation mentioned in the preceding paragraph for the failure of the operation to relieve Raynaud's disease of the hands may be questioned seriously. I believe it probable that the explanation for the divergence of results of operation for Raynaud's disease of the hands and of the feet cannot be explained on the basis that one operation is postganglionic and the other is preganglionic. The work of Dr. Phillips and his associates may clarify the situation.

I would like to have Dr. Phillips answer this question: Is it true from his study that sympathectomy of the preganglionic fibers or postganglionic fibers does not cause an increase in the sensitivity of the arterioles to adrenalin?

Discussion of the paper, "The Isolation of Nicotine from Human Urine," by Dr. Irvine H. Page, Dr. O. M. Helmar, and Dr. Kenneth G. Kohlstaedt, Indianapolis, Ind.

Dr. A. W. Duryee, New York, N. Y.—I have just one little comment to make, namely, that this test gives us a good check on whether our patients with thromboangiitis obliterans have stopped smoking.

Dr. William J. Kerr, San Francisco, Calif.—I would like to ask whether those who chew tobacco have the same or an increased effect.

Dr. Edgar V. Allen, Rochester, Minn.—It would appear that Dr. Page's work is another link in the chain which condemns smoking as a harmful practice for human beings. We know that the inhalation of tobacco may cause sharp increases in blood pressure. We know, also, that the inhalation of tobacco smoke may cause sharp decreases in the surface temperature of the skin of the extremities, indicating vasoconstriction. We know, further, that the inhalation of tobacco smoke may cause visible vasoconstriction in the retina.

We all know that those of us who smoke are subjecting ourselves to a strong vasoconstrictive agent every time we smoke. Those of us who are sensitive to tobacco smoke get a more sharp physiologic response in these various ways than those who are not sensitive to smoke.

However, I should like to point out that it is a long jump to say that because a drug produces a physiologic effect, it is also capable of producing an organic one. For instance, although the inhalation of tobacco smoke causes a sharp decrease in the temperature of the skin of the extremities, so may the ingestion of a glass of cold water or the exposure of any part of the body to cold, and we hardly consider that these things are capable of producing organic changes.

However, there is some evidence, I think, that the use of tobacco is harmful in certain individuals with hypertension, and it certainly seems to be definitely harmful to individuals with thromboangiitis obliterans, because it appears to produce physiologic changes in the arteries by its vasoconstrictive effect, thus adding to the already diminished circulation to the lower extremities.

You may all have read or heard a recent statistical report by Dr. Raymond Pearl which gives a little more grave thought to the subject than I have indicated. If Dr. Pearl's statistics were reported correctly in the news magazines, he has shown that, other things being equal, the smoking of tobacco directly influences longevity. Those who do not smoke live longer than those who smoke slightly. Those who smoke heavily live less long than those who smoke slightly. In other words, there is a direct linear relation between the use of tobacco by smoking and the length of life.

Those of you who have been sitting here all day, smoking one cigarette after another, may go away with this thought in mind.

The work of Dr. Page and his associates is an important contribution to an understanding of physiologic and organic changes which may result from tobacco smoking.

Dr. Page (closing).—I had no intention of suggesting that cigarette smoking was either good, bad, or indifferent. I think, however, that now that we have methods available for studying this problem, it is worth the effort because, after all, if nicotine is excreted in the urine, it may be that a clearance of nicotine may be done to determine the way different people metabolize it.

As to whether chewing tobacco has the same effect as smoking, I should guess that it has. We in Indiana do not chew, so we do not know.

I forgot one thing which is of some interest, I think. We have not actually isolated crystals of nicotine from the blood, but we have separated extracts of blood which seem to contain nicotine. Thus apparently nicotine circulates as any other substance does. It is quite difficult for the body to destroy it, otherwise the liver would presumably have done so completely instead of allowing some to be excreted in the urine.

In Memoriam

JOHN WYCKOFF

1881-1937

John Wyckoff made an important place for himself in American medicine through the force of his character and the originality of his thought. He was a generous and stimulating teacher and a forthright and understanding administrator. In a few brief years he enhanced the position of his school, he assembled a staff of devoted and energetic associates, he made important scientific observations, and he made an impress on the leaders in education in medicine. And all of this he accomplished through the force of his commanding personality—uncompromising, scrupulously just, liberal, and sympathetic in temperament and in conviction. The passing of such a man leaves a void.

Wyckoff was born in the Madras presidency, in India. His education he obtained in the United States. He was a student for two years at Rutgers College, receiving an honorary M.A. in 1920. He was graduated with the degree of M.D. in 1907, from New York University and Bellevue Hospital Medical College. His association there with Doctor Hermann Biggs was important in turning his attention in the direction of the study of cardiac diseases (1909). A little later (1914 to 1915) he joined Doctor Hubert V. Guile in the conduct, under the auspices of the Social Service of the Bellevue Hospital, of the first cardiac clinic (1911) in the United States. This association was, in all likelihood, the determining episode in his life. After the War (he had accepted a commission in the United States Army in February, 1918) he rejoined Dr. Guile (1919) and in the same year he inherited this cardiac clinic. This clinic, under his guidance, became the model for all future enterprises of this nature. Here he demonstrated the variety and thoroughness of the services a cardiac clinic, and by inference, other clinics, can render. Here he carried on his chief scientific work. Here he indoctrinated a great many men in the method and object of medical research. This clinic was to the end, I think, his chief pride. Its creation, in the form he gave to it, was certainly his chief distinction.

The general situation of patients suffering from cardiac diseases was becoming (1915) the concern of several thoughtful physicians in New York, and the result was The Association for the Prevention and Relief of Heart Disease, subsequently The New York Heart Association. Wyckoff became a member of this organization in 1920, being a member also of The Association of Cardiac Clinics, organized in February, 1917, and joined to The Association for the Prevention and Relief of Heart Disease in April, 1923. In both organizations he was active and soon became a leading spirit. In 1923 (November 26), Wyckoff became

John Wyckoff

Chairman of The Association of Cardiac Clinics, succeeding William P. St. Lawrence, and in 1926 (March 18), Chairman of The New York Heart Committee, a position which he held until January 1, 1933. In 1935 and 1936 he was President of The American Heart Association.

Wyckoff was the first, so far as I am aware, who made public use of the realization, growing for several years, that "heart disease" was not a unit. He devised for use in his clinic a threefold form of classification and introduced it in his clinic in 1919. The main heads he proposed were: (1) anatomic, (2) functional, and (3) etiological. Under etiology he provided for the entry of cases resulting from syphilis, rheumatic fever, and senility, and also other acute infections, alcoholism, and "others." In preparing its clinical charts* during 1920 and 1921, a similar plan, independently developed, was adopted by The Association for the Prevention and Relief of Heart Disease.

In this clinic he made the first modern study, utilizing the charts just mentioned, of the incidence† of the various cardiac diseases. To his conviction that this method of accumulating information is useful he gave expression in at least four publications. With this technique he proceeded over a period of years and in association with a succession of colleagues to publish papers on a number of aspects of diseases of the heart, on rheumatic fever, on arteriosclerosis or senescence, on pharmacology, and on treatment.‡ In the brief space available it is impossible to describe his various researches. But it is important in understanding the range and breadth of his insight to quote his remarks on arteriosclerosis: "Many of the questions which we wish to answer could be answered today if the thousands of careful observations made in the various clinics in this city on patients having arteriosclerosis had been collected in a coordinated and uniform way, with the use of definite criteria, and if they had been placed upon a chart which would make them available for statistical study."

"It is my belief that the final answers to most of these questions will come from the careful study of patients in ambulatory clinics over long periods of time, where these patients are not only carefully studied, but where accurate and uniform data are obtained by every available method, and, after being selected, scientifically analyzed."

"Physicians often marvel at the time and patience which a laboratory investigator expends in the development of a proper laboratory technique. Our work, that is, properly coordinated clinical and labora-

*These were reproduced in "The Journal of the American Medical Association" in 1922 (78: 1559).

†Wyckoff and Lingg: Statistical Studies Bearing on Problems in the Classification of Heart Diseases. II. Etiology in Organic Heart Disease. AM. HEART J. 1: 446, 1926.

‡References to these papers are given in "John Wyckoff: 1881-1937." A. E. Cohn: Bull. Inst. Hist. Med. 6: 835, 1938.

tory investigation in chronic disease, demands a technique which is surely as difficult to perfect and the development of which takes years.''*

In the last years of his life, Wyckoff's energies were devoted to problems of education—the selection of students, the construction of the curriculum, the place of medical education in the scheme of things. His approach to the solution of all these matters was as free of preconceptions, as free of predetermining prejudice, as the desire to have it free could make it. If the best students were to be admitted to the schools, they must necessarily be those with the highest scholastic attainments. He found, on analysis, that men who had done best in college made the best medical students. The members that fell by the wayside, in his school, became fewer after scholarship became the chief criterion for admission. It was transparently clear that he valued men for their eagerness to render service, in practice or in teaching, and for their ability to attain high levels of intellectual performance. Under these circumstances he gathered about himself a group of men distinguished for their energy, their disinterestedness, their devotion to his elevated views. The purity of his own ambitions elicited an extraordinary response; men followed where he led and gave him unstinted personal loyalty.

The profession of medicine in the difficult years that lie ahead can ill afford his loss. His open-eyed way of meeting experience had prepared him to lead in ways calculated to understand and to do justice to the interests of the various elements that serve to make up the medical community. He would have known how to adjust the services physicians in their various callings could render to the requirements of men in general. He would have known how to attain the objects at issue without permitting the adjustment to descend to the level of a wrangle. He would have helped to see to it that the complex interdigitating interests became suitably adjusted. He was an administrator who knew that more was wanted in a forward-looking world than to provide merely for the technique of successful manipulation.

It is well not to permit the memory of men like Wyckoff to fade. Their influence, their elevated enterprise, their moral persuasiveness serve to commit men to the most sympathetic service in the interests of society. The realization that Wyckoff had these qualities caused his contemporaries to hold him in high esteem and to give him those opportunities which he used in so distinguished a manner.

Alfred E. Cohn.

*A Consideration of the Possibility of the Prevention of Arteriosclerotic Heart Disease. Tr. Am. College Physicians, Philadelphia 51: 95, 1929.

Department of Reviews and Abstracts

Selected Abstracts

Prognosestudier ved kroniske Hjertelidelser med Henblik pae Elektrokardiogrammernes prognostiske Betydning (The Prognosis in Chronic Heart Disease With Special Reference to the Prognostic Significance of the Electrocardiogram)

By Henning Aastrup, Copenhagen, Denmark

This thesis. written under the direction of Professor Erik Warburg, is an analysis of the cardiologic experience in the Second Division of the Municipal Hospital of Copenhagen between 1924 and 1928. It is a study of 797 patients who were hospitalized and had electrocardiograms, particularly with reference to their status after six to ten years.

The electrocardiographic literature is extensively reviewed. Willius' work is reviewed in detail and criticized. Objection is raised to the lack of information regarding the state of compensation of the patients and it is suggested that Willius' material consists of cases in which the disease was more advanced than in those of other authors. Willius traced only 70 to 80 per cent of his patients. This defect influences prognostic studies unfavorably, as shown by the author's own studies. The exact periods over which Willius' patients have been followed are not indicated. But in spite of these defects the author accepts Willius' conclusion that many electrocardiographic, especially T-wave, changes may be of important prognostic importance in cardiac patients, though Hamman, who examined patients with less advanced heart disease, considered Willius' conclusions much exaggerated.

Other studies reviewed in detail include the important work by Deindl (Arch. f. klin. Med. **178**: 425, 1936). The review is arranged under the following headings: Negative T_1 and T_2; negative T_1 and left axis deviation; low and isoelectric T_1 and T_2; complete and incomplete bundle branch block; bundle branch block with short conduction time; negative T_3; negative and positive T_3 with left axis deviation; complete inversion of Lead III; negative T_3 with right axis deviation; low voltage; changes seen in coronary occlusion; deep Q_3; M- and W-shaped QRS complexes in Lead II; the second positive peak in QRS_3; slurring of the terminal limb of the R-wave in all leads; evolutive changes of the QRS complexes and the normal electrocardiogram.

The study of the literature shows that certain electrocardiographic changes are associated with a relatively high mortality within a relatively brief time. But opinions are divided as to the actual prognostic value of these changes, though they have recently been studied in much detail and in relation to their clinical associations. No electrocardiographic sign has absolute prognostic value. (It seems that denial of the prognostic value of the electrocardiogram is based upon excessive demands. Few clinical signs determine in themselves the prognosis, but when properly interpreted they aid in its formation.)

The contrasting views regarding auricular fibrillation in relation to the prognosis in general, and congestive failure in particular, are sharply drawn. Certainly the prognosis is worse if the ventricular rate is fast and cannot be controlled, probably

also when the ventricular complexes are abnormal, in the presence of extrasystoles, and especially in persons below the age of 20 years. The literature does not show whether the prognosis is better in arteriosclerotic or in rheumatic heart disease.

Then follows an analysis of the author's material. Nearly all the electrocardiograms were taken by Dr. Warburg personally. All terms are carefully defined. The effect of digitalis on the electrocardiogram is discussed, with stress on the prevailing effect on T_3 and T_2.

SYPHILITIC HEART DISEASE

Thirteen per cent of the patients had syphilis. In the general hospital population at the same time the incidence was 9 per cent. A diastolic murmur was heard in all cases in which autopsy later revealed the presence of aortic regurgitation. The diagnosis of syphilitic aortitis is uncertain clinically, though certain anatomically. The author shares the prevailing scepticism regarding syphilitic myocarditis; diffuse syphilitic involvement of the myocardium is very rare. He questions whether syphilis predisposes to the myocardial changes which so often occur in cardiovascular syphilis. He finds that in 80 per cent of cases of cardiovascular syphilis the serologic tests are positive. He stresses the danger of mistaking aortic regurgitation of other origin for that of syphilis, especially if the serologic tests are positive and the causative infection has been latent. Syphilitic aortic regurgitation is rare in patients under 30 years of age.

In about 4 per cent of all autopsies cardiovascular syphilis is present, and among older patients about 75 per cent with the organic changes of syphilis will show syphilitic changes in the cardiovascular system. This incidence can almost certainly be lowered by early and rational treatment, though this conclusion cannot be drawn from the author's own material. Clinically, cardiovascular syphilis occurs in about 25 per cent of persons suffering from late syphilis. Five to 20 per cent of patients with organic heart disease have cardiovascular syphilis. Among cases of aortic regurgitation the incidence of syphilis is high, varying from 30 to 70 per cent, according to how the material is selected. The author's figures and those in the literature agree on these points.

In his pathologic studies he finds that syphilitic aortitis was in no case the sole cause of cardiac hypertrophy. Cardiovascular syphilis was frequently associated with other cardiovascular disease, especially arteriosclerosis, and he discusses whether syphilis predisposes to arteriosclerosis or whether the coincidence is a sign of an inferior vascular system. (There is no proof that this coincidence is more than accidental.)

In syphilis, angina pectoris occurs often at rest, and its prognosis is considered worse in syphilis than in hypertension. He fails to find evidence that syphilis predisposes to hypertension. The coincidence of cerebrospinal and cardiovascular syphilis is 20 to 30 per cent. In 14 per cent of the author's cases there was a rheumatic background.

Of 27 cases of aortic regurgitation, death was caused by heart disease in 25. Sudden death is more common in syphilitic than in rheumatic aortic regurgitation. From a pathologic point of view aneurysms are the direct cause of death in 25 to 30 per cent of those who have them; clinically, the incidence is higher. Uncomplicated syphilitic aortitis is rarely fatal.

The average duration of life in syphilitic aortic regurgitation was three years from the onset of symptoms, but the value of this figure is impaired by the wide spread of the duration, viz., from one month to twelve years. Life is definitely prolonged by adequate treatment.

No electrocardiographic change is pathognomonic of syphilis. Auricular fibrillation occurs in about 5 per cent of the cases and is probably due to some con-

comitant factor other than syphilis. Bundle branch block has a very bad prognosis in syphilis. In 20 cases the T-waves were inverted, and in 4 of these this change preceded other signs of bad prognosis and was thus of real value. In general, the prognosis was bad in cardiovascular syphilis, though worse if the T-waves were negative than if the electrocardiogram was quite or almost normal. Both diagnosis and prognosis were often obscured by coincidental arteriosclerosis. In aneurysm and syphilitic aortitis the cardiac findings, including the electrocardiogram, are not of interest until the disease has extended to the coronary orifices or the aortic valves.

RHEUMATIC HEART DISEASE

In 223 (28 per cent) of the cases there was evidence of rheumatic infection, past or present. Aortic regurgitation, aortic stenosis, and mitral stenosis are the only lesions which can be diagnosed with certainty. It is difficult to determine whether old calcified valves are the result of a chronic infection with secondary calcification or of pure arteriosclerosis. In recent lesions the larger verrucous processes may be caused by recurrent rheumatic endocarditis, simple thrombi, or subacute bacterial endocarditis, and the smaller ones by recurrent rheumatic endocarditis, so-called terminal endocarditis, or small aseptic thrombi. After an extensive review of the literature he leans to the view that old stenosing lesions of the aortic valve (Mönckeberg) are as a rule primarily inflammatory with secondary calcification. Mitral stenosis was diagnosed only in the presence of the typical murmur. Neither clinically nor anatomically was it possible to differentiate between mitral stenosis and mitral stenosis and regurgitation. In spite of Dressler and Fischer's work, no effort was made to diagnose lesions in the right side of the heart (most of the diagnoses were made before 1929, however). A systolic murmur at the apex is a quite reliable sign of mitral regurgitation, but it has been present when the valves were normal, and absent when they were diseased. Mitral regurgitation was not the cause of death in any of the author's cases. However, some modern authors consider these views too extreme. The typical murmur of mitral stenosis the author found to be a constant and pathognomonic sign of the lesion. Mitral stenosis does not develop diagnostic signs until three to six years after the initial infection. Rheumatic aortic lesions almost always show signs of stenosis. Flint's murmur is rarely accompanied by a thrill and the second sound is never split. It was found in 7 of 19 cases of syphilitic aortic regurgitation, in none of which was mitral stenosis present at autopsy. While it contains nothing new, this is an excellent discussion of the criteria for diagnosis and the accuracy with which valvular lesions can be diagnosed. The strict criteria resulted in a higher incidence of combined mitral and aortic lesions in the pathologic than in the clinical analysis. Rheumatic valvular defects were diagnosed in 131 cases, in 127 of them, clinically; in 4 the diagnosis was missed clinically for good and sufficient reason. Without reserve the author seems to accept symphysis pericardii as rheumatic in nature. Sixty-nine per cent of the patients had mitral stenosis, 17 per cent mitral stenosis and aortic lesions, 14 per cent aortic lesions (15 regurgitation and 4 stenosis); 61 per cent were between 20 and 50 years of age, 20 per cent were past 50, and 19 per cent were below 20 years of age. Aortic regurgitation was rare in the young. Women prevailed among those having mitral lesions (69 to 43) and men among those with aortic lesions (18 to 1). Sixty-three and four-tenths per cent gave a history of polyarthritis, 5.3 per cent of chorea, and 31 per cent gave no rheumatic history. The average age at the first attack of rheumatic fever was 17 years; among those under 20 years of age it was 11, and among those above 50 it was 25. Pulmonary complications were frequent; 47.6 per cent presented them at the time of the first electrocardiographic examination. Respiratory infections were commonly the cause of heart failure. Cardiac asthma was more common in rheumatic heart disease than is generally assumed. Among 84 patients

with valvular disease who were followed till they died, 46 showed signs of embolism at one time or another, but many who did not die when embolism occurred lived for several years afterwards. Most of the emboli which were diagnosed clinically occurred in cases of auricular fibrillation. Angina pectoris occurred five times with aortic lesions, never with mitral lesions. Seven out of 90 patients with mitral stenosis had a systolic blood pressure of 160 or more, and all of these were more than 45 years of age. The same was true in 2 of 18 cases of mitral stenosis and aortic lesions, in 1 of 4 cases of aortic stenosis, and in 5 of 15 cases of aortic regurgitation. Hypertension did not add to the gravity of the prognosis.

Ninety per cent of the patients with rheumatic heart disease died from their heart disease, a great many of them with some terminal infection (bacterial endocarditis, rheumatic infection, colds, etc.). Subacute bacterial endocarditis was especially common in aortic lesions in men. Two patients with aortic stenosis died suddenly. All of these findings are discussed in the light of extensive collections of data from the literature.

In 43 patients dying from rheumatic heart disease the age at the time of the first rheumatic infection was known. On an average they lived for twenty-five years. The average age at death in 50 cases of mitral stenosis was 42.7, in 18 cases of mitral stenosis and aortic lesions 44.7, in 16 cases of aortic lesions 55 years, and in the whole group of 84 cases 45.5 years. Comparing his experience with that of others, he points out that the relatively low age in the series reported by DeGraff and Lingg (33 years) may be due to the facts that the patients as a whole were relatively young, and that only 73.3 per cent of the 1633 patients had been traced (the author traced all of his but one). The older the patient is at the time of his first attack, the shorter his life expectancy. This may be because this series does not include the children who died within a few years of their initial infection. The number of attacks of rheumatic infection and the type of valvular lesion do not seem to affect the prognosis.

Auricular fibrillation occurred in 71 per cent of the patients who were followed till they died. It occurred late in the course of the disease. In the author's entire series it was as common in aortic as in mitral lesions, but among those who died it more frequently accompanied mitral lesions. Auricular fibrillation and subacute bacterial endocarditis coincided very rarely. Auricular fibrillation was rare in youth. It was relatively often associated with changes in the ventricular complexes in the cases of aortic regurgitation, but with mitral stenosis such changes (except right axis deviation with or without negative T_3) were rare.

The cases with normal rhythm were analyzed in detail but offered nothing of special interest.

Of 56 patients with rheumatic heart disease and auricular fibrillation, 84 per cent died from cardiovascular complications after an average of thirty months. When all of these patients have died, they will have survived, on an average, three to four years. However, in any statistical study of this kind the result will depend upon the nature of the material, especially with respect to how many patients below the age of 20 years it includes, and the number of cases of terminal and "catastrophic" auricular fibrillation. This again will depend upon how closely the patients have been followed in the terminal stages. The author next excludes the patients with a very unfavorable prognosis, then adds to the lifetime of the others the period between the discovery of the auricular fibrillation and the first electrocardiogram, and then finds that the average period of survival for 42 patients was close to five years. Sixteen of these died within three years of the discovery of auricular fibrillation, but only 5 of them from congestive failure; the others died from embolism and other dramatic events. This experience led the author to a less pessimistic view on the prognosis of auricular fibrillation.

In decompensated patients the prognosis was determined by the cause of the congestion; if this was transitory, as in the case of acute respiratory infections, the prognosis might be quite good. Patients with auricular fibrillation, right axis deviation, and a negative T_2 died sooner than those with normal ventricular complexes. Cases of rheumatic heart disease taken as a whole, a negative T_1, with or without other T-wave changes and incomplete bundle branch block, gave a bad prognosis, for all the patients with these lesions had died, while almost all of those with normal electrocardiograms survived. This distinction was less marked among the very old patients. The prognosis when the T-waves were isoelectric was somewhat better than when they were negative. Most of those patients with negative and isoelectric T_1 waves who died within three years presented other signs of a bad prognosis also. Patients with right axis deviation and a large P_2 showed a tendency to auricular fibrillation and had a greater death rate than those with other minor abnormalities. The prognosis of negative T_3 was worse if right axis deviation was also present; in most of the patients who died there were also other signs of a bad prognosis. Likewise, it was worse if T_2 also was negative, but a definite statement on this point was difficult because in many of the patients this change might have been produced by digitalis. Of the group of patients with rheumatic valvular disease and T-wave changes but without complete A-V block or auricular fibrillation, 71 per cent died, on an average, twenty-eight months after they were first observed. However, the author believes that the prognosis in cases in which there were T-wave changes would be better if those cases were excluded in which, on clinical grounds alone, the prognosis was bad. Again he mentions that Willius' unfavorable experience with T-wave changes could be explained by a high incidence of decompensation cases. Both Willius and others found that the various T-wave changes are not in themselves incompatible with several years of life. They often precede clinical signs of a bad prognosis, especially in chronic, rheumatic, aortic lesions. On the whole, he decides, the prognosis in cases in which there are T-wave changes is better than is generally assumed, though not as good as when the electrocardiogram is normal. The electrocardiogram is of real prognostic value. Right axis deviation with negative T_3 had about the same prognostic value as left axis deviation with negative T_1.

HYPERTENSION AND DEGENERATIVE HEART DISEASE

If these patients develop congestive failure, tests of renal function are of less value. Also, percussion is of limited value in determining the size of the heart. The author seems to use the term "degenerative heart disease" in a more comprehensive sense than do most American authors.

Of 154 fatal cases of essential hypertension, 64 per cent of the patients died from heart disease (50 per cent of this number from congestive failure, 25 per cent suddenly), 17 per cent from apoplexy, 4 per cent from uremia, and 16 per cent from other noncardiovascular causes. These figures compare interestingly with those of other investigators, especially those of Bell and Clawson. The low incidence of uremia is striking, but is explained by the rigid exclusion of nephritic hypertension from the series.

The apical systolic murmur, so common in hypertension, was studied especially. It was found in 22 patients who later came to autopsy. In 4 the valves were definitely deformed, 7 had slight changes in the form of calcification of the bases of the valves, and 11 were entirely without valvular changes. Most of the hearts were hypertrophied but there was no proportion between the degree of hypertrophy and the degree of hypertension. Most of the patients with hypertension who died from congestive failure had marked coronary sclerosis and myofibrosis. Definite myomalacia was found in 15 of 94 patients who came to autopsy.

There were 69 cases of angina pectoris, and in 32 (including 2 in women) there was coronary thrombosis, fresh or old. Fourteen had diabetes (this statement was not amplified by further diagnostic detail).

Of the 19 patients with coronary thrombosis, 16 had died. Eleven could date their first attack. Five died within a month, and on an average (including 3 survivors) they had survived for two years. The survivors had survived nine, eight, and six and one-half years, respectively. The average period of survival in any such series depends on how many patients are included who died immediately or soon after an attack. It is naturally longer if it is limited to patients who have survived for at least two months. First attacks of coronary occlusion are rarely fatal. During the acute stage the prognosis is best evaluated by considering the general state of the patient, the droop in blood pressure, and the degree of fever. Paroxysmal ventricular tachycardia and arborization block he found to be grave complications. There was no marked difference in prognosis between anterior and posterior occlusions. He did not say whether a rapid return of the electrocardiogram to normal may be considered a favorable sign.

Of 50 patients with angina pectoris, 41 had died, 34 of them from heart disease (4 in status anginosus, 2 of apoplexy). Thirty-seven about whom information was available had survived from two months to thirteen years, on an average about four and one-half years. The 9 who survived had had the disease, on an average, ten years. Those with hypertension had all died. Only 3 of the 50 had quite normal electrocardiograms, rather a small number. None had auricular fibrillation. Twenty-two had a negative T_1; 86 per cent of these had died from cardiovascular disease after an average period of twenty-five months. Of the 3 with normal electrocardiograms, 2 were still alive. Thus the normal electrocardiogram seemed to offer a better prognosis. The prognostic value of the electrocardiogram was definitely less above the age of 63 years. Below that age the value was less in angina pectoris than in other conditions, because these patients are subject to sudden changes for the worse, especially coronary occlusion. On the other hand, in angina pectoris the electrocardiographic changes were relatively often the only sign, apart from the pain, which indicated a change in prognosis.

In 154 fatal cases of hypertension the largest number of patients died between the ages of 60 and 70 years; only 8 per cent were below 50, and 33 per cent were above 70 years of age.

The result of prognostic studies in hypertension depends upon whether the group chosen consists of ambulatory or hospital patients. If the symptoms are severe enough to demand hospitalization, life expectancy is generally limited. In all groups, men showed the highest death rate. Schwensen (Ugesk. f. laeger **98**: 1264, 1936) followed 159 (57 of whom were women) Danish hospital patients with hypertension. After seven and one-half years the death rate was 74 per cent for the men and 50 per cent for the women. The prognosis for the men seemed to be independent of the height of the blood pressure. For the women there was a definite relation between the two, for among 21 with a systolic blood pressure above 225 the death rate was 71 per cent, among 39 with systolic pressures of 200 to 225 it was 44 per cent, and among 22 with systolic pressures between 170 and 199 it was 32 per cent. Roslin (Acta med. Scandinav. **83**: 41, 1934), for 8 years, followed 102 patients receiving sickness benefits for essential hypertension. Seventy-two were still alive at the end of the period. Of 205 with essential hypertension and cardiac symptoms 53 per cent were alive after eight years.

Of Aastrup's 186 patients, 27 per cent had normal electrocardiograms, 19 per cent auricular fibrillation, 2 per cent complete A-V block, 11 per cent left axis deviation with negative T_1; 20 per cent a negative T_1 with or without other T-wave changes, 2 per cent negative T_2 and T_3, and 7 per cent left axis deviation.

Of 36 patients with auricular fibrillation and hypertension, 78 per cent died of cardiovascular causes after an average of thirty months, and 8 per cent lived after an average of eight years. Of 26 patients with degenerative heart disease with auricular fibrillation but without hypertension 58 per cent died after an average of nineteen months. Sixty-nine per cent of all the patients with auricular fibrillation died from cardiovascular causes after an average period of eighteen months, and 19 per cent survived for an average period of seven years. These figures correspond closely with those for mitral stenosis. But three-fifths of the patients with hypertension and degenerative heart disease were above the age of 63 years, whereas only one-twelfth of those with mitral stenosis had passed this age. Considering only the patients below the age of 63 years, the average period of survival (about four years) was about the same for degenerative and mitral heart disease. Nearly all the patients less than 63 years old who had died in less than three years died from special complications, or there was evidence that the arrhythmia had existed for a considerable time before the first electrocardiogram was taken. In this group also, therefore, the average duration of auricular fibrillation is considerably above four to five years when the patients with special complications are excluded. The "catastrophic" type of auricular fibrillation which was noted in mitral stenosis was not seen in cases of hypertensive or degenerative heart disease. The course of the auricular fibrillation was more favorable when the ventricular complexes were normal. One patient with auricular fibrillation had no other signs of heart disease and was considered as belonging to the group in which auricular fibrillation is without prognostic significance.

A relatively large number of patients with hypertension, regular rhythm, and inverted T-waves died within a relatively short time, but among those with normal electrocardiograms few died from heart disease during the period of observation. T-wave changes frequently preceded other signs of an unfavorable prognosis. Of those with normal electrocardiograms who died, a disproportionate number were above 63 years of age, and consequently the prognostic value of the electrocardiogram was greatest below that age. Among the cases with T-wave changes, the addition of left axis deviation did not seem to aggravate the prognosis.

Among 27 patients with hypertension and late syphilis the death rate was about the same as among those with hypertension and no syphilis. Among the adults with cardiac symptoms and rheumatic history but without certain signs of valvular affections a relatively large number had hypertension, including all of those with a negative T_1, and most of those with auricular fibrillation.

Thirty-nine patients were observed during their first attack of rheumatic fever. During the first five years none of them died. During the second five years, 2 died from heart disease following another attack of carditis or from ulcerative endocarditis.

One patient had bundle branch block and a short A-V conduction time. The course was favorable as long as the patient was observed, and the author takes a view of this condition which is somewhat more optimistic than that of Wilson.

Finally, the author concludes that in general his findings conform with the prevailing views expressed in the literature. He emphasizes the part played by respiratory infections in precipitating congestive failure. When the T-waves changed, the heart generally deteriorated, though there was no absolute parallelism between electrocardiographic changes and the progress of chronic heart disease.

Certain T-wave changes have ominous significance, varying with the form of heart disease. The prognostic value is greatest between the ages of 20 and 63 years. If electrocardiograms were taken more commonly in the routine follow-up studies of patients with heart disease their prognostic value would unquestionably be enhanced. Especially, if patients could be followed through to the end one would learn much of the prognosis at the onset of the changes.

Above the age of 63 years the prognostic value of the electrocardiogram is not so great. Many old persons will long survive with marked changes, and many have normal electrocardiograms shortly before they die. Probably the cardiac changes which produce abnormalities of the electrocardiogram develop so slowly in old age that the heart has a chance to compensate for them, while, on the other hand, even a relatively well-preserved myocardium in old persons has but a limited reserve which is easily exceeded in case of sickness.

Below the age of 20 years most cardiac patients have rheumatic heart disease, and death is caused by acute carditis; the prognosis is then determined by its occurrence.

Among cardiac patients between the ages of 20 and 63 years, with normal electrocardiograms, the course was on the whole favorable during the period of observation, except among those with syphilitic aortic regurgitation, and even here there were some irregularities of the R-waves in those who died. T-wave changes generally mean that the process is more advanced and that the period of survival is limited, but, on the other hand, the author believes that these changes occur earlier than is generally assumed. Between the upright and the negative, stand the isoelectric T-waves; their significance depends upon the rate at which the wave is changing. The prognosis of inverted T-waves in women with hypertension is best.

Functional tests the author considers of limited value because they are so often affected by extraneous factors.

Another reason why the electrocardiogram has so great a prognostic value is that most cardiac patients die from their heart disease, and usually from congestive failure. Among the patients who died from increasing failure and in the group in which the largest number of patients had died from congestive failure the course of the disease corresponded best with the prognosis indicated by the electrocardiogram.

The operative death rate is greater among patients with abnormal than with normal electrocardiograms. The prognosis is about the same in complete and in incomplete heart block; these usually, but not always, occur during the last stages of chronic heart disease. If the clinical condition does not change in a year or two, the prognosis is much improved. Arborization block carries about the same prognosis as bundle branch block. In coronary occlusion these changes are a very bad sign. Intraventricular block with a wide S_1 is evaluated differently by various authors; some consider it of no consequence, and others think that it is as serious as other forms of bundle branch block; certainly it seems to be of no consequence in younger persons without marked cardiac symptoms. Low voltage is of no consequence apart from heart disease, but in congestive failure it is a serious sign if it does not change on treatment. A deep Q_3 is commonest in angina pectoris and is then usually associated with other changes. Many patients with a deep Q_3 die suddenly, but the average duration of life of patients with this complication has not been determined. When it is found in healthy persons the heart usually lies in a transverse position.

The significance of inversion of T_2 and T_3 is similar to that of inversion of T_1, but is less serious. An isoelectric T_3 is of no consequence. Left axis deviation with T_2 higher than T_1 is found in real heart disease, and if in such cases S_2 is deep and T_1 low or isoelectric the heart is almost certainly diseased, but for a proper interpretation of these tracings it is necessary to know the position of the heart, preferably from roentgenologic examination. Complete inversion of the complexes in Lead III is seen mostly in obesity.

As his main conclusion the author finds that the greatest prognostic value of the electrocardiogram is in cases of chronic heart disease in which definite clinical signs of prognostic value have not appeared or are difficult to interpret.

Dr. Aastrup's book is an ambitious piece of work, beautifully done. Throughout, the author restrains himself to such conclusions as are warranted by his as-

sembled facts. He has been fortunate in combining with indefatigable industry and his own common sense the counsel of one of the most clear-thinking cardiologists in Europe. Unfortunately the book will probably never reach as wide a circle of readers as it deserves, for it is published as a thesis in a very limited edition in Danish.

JULIUS JENSEN.

Paff, George H., and Johnson, J. Raymond: The Behavior of the Embryonic Heart in Solutions of Ouabain. Am. J. Physiol. 122: 753, 1938.

The forty-eight-hour embryonic chick heart exposed to a 1:300,000 dilution of ouabain undergoes A-V block, ventricular stoppage, and finally sino-atrial stoppage. The block is most constant as to time of appearance. Higher dilutions or lower temperature greatly delays these effects. These reactions are reversible since a quiescent heart can be revived by washing with Tyrode's solution. The cause of block apparently lies primarily in depression of irritability.

AUTHOR.

Cossio, P., and Martinez, F.: Graphic Registration of the Percussion Sound of the Chest. Rev. argent. de cardiol. 5: 1, 1938.

The percussion sounds recorded by means of a microphone (30 cm. from the chest wall) showed characteristics allowing recognition as regards sonority, dullness, and tympanism. The records show that both lung resonance and hepatic dullness are due (1) to vibrations originated by the striking finger and (2) to the movement of chest wall and underlying structures interfering with each other. In the case of the normal lung resonance the former only last for a brief initial period and the latter integrate the whole duration (0.4 to 0.5 second) of the acoustic phenomenon, the last portions of the vibratory phenomenon being formed only by them. In the case of hepatic dullness, the finger and chest wall vibrations predominated, but there were also present some lung vibrations due to the pleximeterlike action of ribs.

In six cases the heart area was traced by percussion with the sounds recorded as described, and the results were compared a posteriori with the x-ray pictures. The following findings were made:

The superior limit of the liver was marked too low in front of the mid-axillary line but sometimes at the right heights are even higher. Right of the sternum there was no change in resonance even though the right auricle surpassed its border in 1.5 to 3 cm.; only in cases of heart enlargement to the right can a lessened resonance be found to the right of the sternum. The left border of the heart at the level of the fourth or fifth interspace was marked from 1 to 2 cm. toward the left from the true place. Coincidence or error in the other direction was exceptional.

On the left parasternal line, diminution of resonance only occurs below the superior part of the left heart border and only coincides when this portion is formed by the pulmonary conus due to enlargement of the right ventricle.

The differences between the limits as marked by percussion and the real situation are explained by the deep location of the organs and also by the curvature and regional peculiarities of the chest wall.

AUTHOR.

Bean, William Bennett: Infarction of the Heart. II. Symptomatology of Acute Attack. Ann. Int. Med. 11: 2086, 1938.

The incidence of cases of cardiac infarction coming to autopsy increased fourfold in the later of two fifteen-year periods investigated. Of 300 patients on whom autopsy was done, 114 died within six weeks of the initial infarction; 75 patients had multiple lesions and survived more than six weeks; old scars were found in 111 cases.

Correct diagnosis was rare in the absence of pain. Mistaken diagnosis was usually confused by the symptom of pain. One-third of the cases showed signs of congestive failure before acute infarction. A prodromal period of pain occurred in 16 per cent of acute attacks. Pain and congestive failure occurred together in many cases. Dyspnea was the most frequent symptom and where associated with a sense of constriction merged into the ill-defined domain of pain. No constant morphologic finding could account for the vagaries of pain, its presence or absence, its location and radiation. Some evidence indicated it to be conditioned by individual differences, a cerebral rather than cardiac function. In acute cases without pain the onset was frequently characterized by sudden accession of failure, less often by central nervous symptoms (syncope, weakness). Tachycardia, enlarged heart, feeble heart sounds, and arrhythmias were frequently encountered. Pericardial friction rubs were heard in 41 per cent of cases with acute pericarditis. The arterial blood pressure was found to remain elevated in a large number of cases, though the majority showed declining levels. Fever and leucocytosis, although usually present, were absent in an appreciable number of cases.

Electrocardiographic studies revealed prolonged P-R interval in 25 per cent and prolonged QRS intervals in 46 per cent of all cases. These conduction defects were almost twice as common in predominantly right artery involvement as in left. The diagnosis of anterior infarction was usually correct, but one-fifth of those diagnosed posterior infarcts were wrongly localized. A large Q-apex invariably indicated posterior location and absent Q-apex invariably indicated anterior infarction.

AUTHOR.

Bean, William Bennett: Infarction of the Heart. III. Clinical Course and Morphological Findings. Ann. Int. Med. 12: 71, 1938.

No specific prognostic gauge was found to be valid in an individual case. Congestive failure and shock followed in more than half of the acute attacks. Enlarged liver and jaundice were observed in a small proportion of cases. Peripheral embolism was found most frequently in the second, third, and fourth weeks. Many incidents considered clinically to be embolic were found to depend on local vascular faults. Causes of death were investigated, and the predisposing influence of syncopal attacks was noted in cases of sudden death. Seasonal variation of death was in part influenced by seasonal fluctuation in incidence of acute attacks.

The left coronary tree was seriously involved in 84 per cent of cases, the right in 21 per cent. Nine cases of ectopic infarction appeared. Twenty per cent of the infarcts followed arterial narrowing without thrombosis. In four cases no arterial damage was detected. Eight cases of coronary anomalies were found, one with a small coronary aneurysm. The heart was enlarged in 83 per cent of the cases. The largest hearts were found in hypertensives. Ventricular mural thrombi were found in nearly half the cases; emboli were detected twice as frequently in instances of right ventricular thrombi as in cases of mural thrombosis of the left ventricle. Some thrombi were present three years after acute infarction. Embolism was most frequent when the thrombus was attached to the interventricular septum. Ventricular aneurysm was found in 10 per cent of the cases and appeared as early as the seventeenth day after infarction. There were three cases of extensive calcification of scars. Spontaneous rupture of the ventricle occurred in seventeen cases. One survived rupture eight days. In one case an aneurysm was ruptured by a needle. Four cases of coronary embolism from friable valvular vegetations were found, and there was one probable case in addition. There were two auricular infarcts. Pericarditis was found in 32 per cent of the cases and an effusion of 50 c.c. or more, in 15 per cent. Hydrothorax was frequent, and in many cases was greater on the right.

AUTHOR.

Kinsella, Ralph A., and Muether, R. O.: Experimental Streptococcic Endocarditis. Arch. Int. Med. 62: 247, 1938.

Seventeen dogs were subjected to operation whereby the mitral valve or the chordae tendineae were cut. All these animals were then fed with living cultures of nonhemolytic streptococci, either mixed with food or by stomach tube. Ten of the animals became sick, displayed positive results of blood culture, and died. At autopsy these infected animals had bacterial endocarditis. The bacteria in the vegetations were determined to be identical with those that had been fed to the animals.

Streptococcic endocarditis can be produced in dogs with injured cardiac valves by feeding them streptococci.

The fact is thus established that bacteria entering the animal body through the mouth may become implanted on an injured area within the body. The exact route which these bacteria follow is not determined.

AUTHOR.

Taussig, Helen B., Harvey, A. McGehee, and Follis, Richard H., Jr.: The Clinical and Pathological Findings in Interauricular Septal Defects. A Report of Four Cases. Bull. Johns Hopkins Hosp. 63: 61, 1938.

The essential pathological findings are a widely patent foramen ovale, great dilatation and hypertrophy of the right auricle and the right ventricle, and relative enlargement of the pulmonary artery and its branches and a small ventricle and aorta. This syndrome is usually associated with some condition, such as a left side valvular lesion or hypertension, which causes increased pressure in the left auricle. The characteristic enlargement of the right auricle and ventricle may occur, however, in the absence of any demonstrable increased strain on the left side of the heart.

On physical examination the significant findings are as follows: A frail individual with left-sided chest deformity, marked cardiac enlargement of the right auricle and the right ventricle, and usually a harsh systolic murmur and thrill in the second and third left interspaces; clubbing and cyanosis are absent.

The x-ray picture shows four distinctive features, i.e., great enlargement of the right side of the heart, a prominent pulmonary conus, a small aortic knob, and increased hilar shadows.

The sequelae which are of such common occurrence as to be of diagnostic aid are cardiac arrhythmias, superimposed rheumatic infections, pulmonary infections, paradoxical emboli, and the freedom from subacute bacterial endocarditis.

AUTHOR.

Lyon, James Alexander: The Interpretation of Certain Cardiac Signs in Children Bol. Soc. cubana de pediat. 10: 402, 1938.

At the Cardiac Clinic of The Children's Hospital, where a large number of children have been followed for a period of years, it has been found that the cardiorespiratory and the constant or occasional systolic apical murmur occurring in a well-nourished, nonrheumatic child are not evidence of rheumatic heart disease. A child's activities should not be restricted on the basis of these murmurs alone.

It has been observed that among those patients who have an attack of rheumatic heart disease, a small number will become clinically free of all symptoms and signs of the disease, including murmurs.

The myocardium in some cases may be extensively involved without an accompanying valvular pathology. Cardiac dilatation alone may produce murmurs that are clinically indistinguishable from those produced by mitral stenosis and incompetency and by aortic stenosis and regurgitation. In certain cases there will be a concurrent disappearance of both cardiac dilatation and valvular murmurs.

A child who has a persistent systolic apical murmur following a single attack of rheumatic heart disease should not have his activity curtailed, provided that his response to effort is normal and there is no evidence of active infection.

AUTHOR.

Leiter, Louis: Unusual Hypertensive Renal Disease. J. A. M. A. 111: 507, 1938.

Three cases are reported of organic kidney disease associated with hypertension with complete pathologic studies.

The first case is one of thromboarteritis obliterans of small renal arteries. Acute hypertension and failure of the left ventricle were present for several months without significant impairment of renal function.

In the second case chronic arteriosclerotic occlusion of the main renal arteries was associated with chronic hypertension, renal insufficiency, retinal arteriosclerosis, and contracted kidneys.

These two cases are analogous, clinically, to the Goldblatt experimental hypertension.

In the third case there were various congenital anomalies of the urinary tract leading to marked atrophy of both kidneys. The causes of the hypertension in this patient were uncertain. Certain congenital anomalies of the urinary tract are apparently regularly associated with hypertension, while other types show a much lower incidence. With both types the kidneys may be markedly contracted. The reason for the presence or absence of hypertension is unknown.

Chronic pyelonephritis is commonly productive of hypertension. The exact mechanism is not clear.

NAIDE.

Hausner, E., and Allen, E. V.: Thrombo-Angiitis Obliterans of the Brain. Proc. Staff Meet. Mayo Clin. 12: 653, 1937.

Thromboangiitis obliterans usually affects arteries of the extremities. Twenty-three instances of involvement of the blood vessels of the brain have been reported in the literature and fourteen have been encountered at the Mayo Clinic in the study of 500 cases of thromboangiitis obliterans. Of the cases reported in the literature, there were six in which the clinical history of organic changes in the peripheral vessels made them acceptable as true examples of thromboangiitis obliterans with involvement of the cerebral vessels and in which results of necropsy examination of the brain were reported. In one case embolism was said to be present; in two cases the cerebral arteries were involved by both inflammation and sclerosis; in two cases there was sclerosis only; and in two cases the inflammatory processes characteristic of thromboangiitis obliterans of the extremities were found. In the fourteen cases observed at the Clinic the diagnosis of thromboangiitis obliterans of the peripheral arteries was proved by microscopic examination, and the clinical history and findings were characteristic. Neurologic manifestations disappeared and recurred rather rapidly in several cases. Hemiplegia, which was the most outstanding manifestation, may last for several years or days and later another attack of hemiplegia may occur. Associated with the hemiplegia there may be symptoms such as confusion and irrational behavior. In three instances hemiplegia preceded the symptoms of involvement of the peripheral arteries. Disorders of behavior and psyche are not unusual. A very common complication is hemianopsia. In this study of 500 cases of thromboangiitis obliterans there was evidence of cerebral involvement in about 3 per cent. This study emphasizes that cerebral lesions in thromboangiitis obliterans occur and that peripheral thromboangiitis obliterans may be the least serious part of a disease which may disable or terminate life as a result of involvement of such vital structures of the brain and heart.

AUTHORS.

Holman, Russell L., and Self, Edward B.: The Ability of Lymph to Maintain Viability in "Devascularized" Lymph Nodes. Am. J. Path. 14: 463, 1938.

Studies were made on the ability of lymph per se to keep tissues alive. The vascular and lymphatic connections of popliteal nodes in dogs were completely severed and the nodes replaced in the popliteal space. All the nodes underwent massive necrosis.

When the authors severed all blood vascular connections but left one or more afferent and one or more efferent lymphatics intact, the nodes remained viable. The observations imply a nutritive function on the part of lymph.

NAIDE.

Veal, James Ross: Direct Visualization of the Axillary and Subclavian Veins. Radiology 31: 183, 1938.

A method of directly visualizing the axillary and subclavian veins by use of thorotrast is presented.

A number of normal and abnormal venograms are included.

The value and limitations of this method are discussed.

NAIDE.

Bowesman, Charles: Intra-Arterial Glycerin Treatment of Elephantiasis. Brit. J. Surg. 26: 86, 1938.

When glycerin is placed in contact with living tissue, it causes a movement of tissue fluid from the tissue spaces toward the vessels or region in which the glycerin is placed.

Injection of 2 to 3 c.c. of sterile 10 per cent glycerin into the femoral artery, repeated at weekly intervals, affords a simple and safe method of alleviating to some extent elephantiasis of the leg due to filaria. Intravenous injections produce an effect on the limb, though less marked.

Early cases showed marked reduction in the size of the limb. Late cases showed some improvement. The dull aching discomfort is in all cases much lessened.

Five months after treatment patients showed limbs which either had the same size as at the end of the treatment or remained smaller than before the commencement of treatment.

NAIDE.

Lueth, Harold C., and Hanks, Thrift G.: Unusual Reactions of Patients With Hypertension to Glyceryl Trinitrate. Arch. Int. Med. 62: 97, 1938.

Severe reactions not infrequently follow the administration of glyceryl trinitrate to patients with hypertension. The nature and frequency of these reactions were studied. Fifty patients with essential hypertension or hypertensive heart disease were selected from the outpatient dispensary. A chemically assayed solution of glyceryl trinitrate was carefully administered directly under the patient's tongue with an accurately graduated pipette. All tests were made under standard basal conditions, and frequent blood pressure readings were made. Nine patients (18 per cent) showed reactions, i.e., nausea, vomiting, syncope, collapse, and involuntary passage of urine and feces. These followed doses as low as 0.24 mg. ($\frac{1}{300}$ grain) and were more severe when the patient was sitting up than when he was recumbent. All the patients recovered completely within an hour. Four well-known clinical procedures were applied in these cases in the hope of determining unusual vasomotor lability. The Hines-Brown test, the histamine flare test, and changes in the pulse volume and observations of the capillaries of the skin were of no assistance in predicting these reactions.

AUTHOR.

Book Review

HEART FAILURE: By Arthur M. Fishberg, M.D., Associate in Medicine, Mount Sinai Hospital, New York City. 788 pages, illustrated, cloth $8.50. Philadelphia, 1927, Lea and Febiger.

This book represents a summary of all the important knowledge concerning circulatory failure. It includes not only an excellent presentation of the clinical aspects of the subject but a correlation of these with the advances made during recent years in the pathology, biochemistry, and especially in the physiology of the subject. Beginning with a classification of circulatory syndromes into heart failure and peripheral failure, there is a brief mention of the subdivisions of each, followed by a series of chapters devoted to the various circulatory functions such as cardiac output, velocity of blood flow, blood volume and arterial and venous pressures. The several following chapters are concerned with such important manifestations of heart failure as edema, dyspnea, and cyanosis. The relation of heart failure to disorders of the lungs, kidneys, and nervous system is then considered. After a section in which the mechanism of heart failure is summarized, the important aspects of cardiac enlargement, gallop rhythm, cardiac murmurs, and pain arising in the heart are discussed. Several chapters follow dealing with the various conditions under which left-sided and right-sided heart failure occur. The next section, which deals with peripheral circulatory failure, is especially good in that the great importance of this syndrome in medical as well as in surgical disorders is adequately emphasized. The final sections of the book are concerned with therapy.

It is not possible in the brief space available for review to do justice to this excellent book. Every chapter reveals evidence of extraordinary scholarship. The author has an unusually broad knowledge of the subject and displays deep insight into the problems discussed. Like all good books, this one has a few weak points. Most students of heart failure will not agree with the author's statement that this disorder is always characterized by congestion as the dominant manifestation. A seizure of unconsciousness due to heart block is surely a form of heart failure, but congestion is the least important feature of the attack, the main disturbance being an inadequate blood supply to the brain. However, the author is quite correct in emphasizing that in the ordinary forms of heart failure congestion back of the failing chamber rather than inadequate output of the failing chamber is the cardinal feature. One can also take exception to certain points in the author's classification. For instance, the author classifies the heart failure produced by paroxysmal tachycardia as "hypodiastolic" failure resulting from inadequate filling as the result of the rapid rate. Actually, when failure does supervene in such cases it is associated with cardiac dilatation and hence the condition is more analogous to the ordinary "hyposystolic" failure than to the "hypodiastolic" failure due to such disorders as pericardiac effusion. However, no classification can be perfect and Fishberg's is probably as good as any that can be made and has the advantage of simplicity. The flaws in the book are of minor import and are few, while the advantages are many. The practical sections dealing with diagnosis and therapy are excellent, while the sections concerned with discussions of the theoretic aspects are perhaps even better. Fishberg's book will prove a valuable guide for the student beginning his contacts with cardiac disease, for the busy practitioner interested only in practical knowledge, and for the internist who already knows heart disease but wants to know it better. Every investigator in the field of cardiovascular disease can profit by reading this splendid book.

TINSLEY R. HARRISON.

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The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

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